

Nasal and Pharyngeal Concentrations of Peramivir Following Intramuscular and Intravenous Administration in Healthy Volunteers

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Introduction

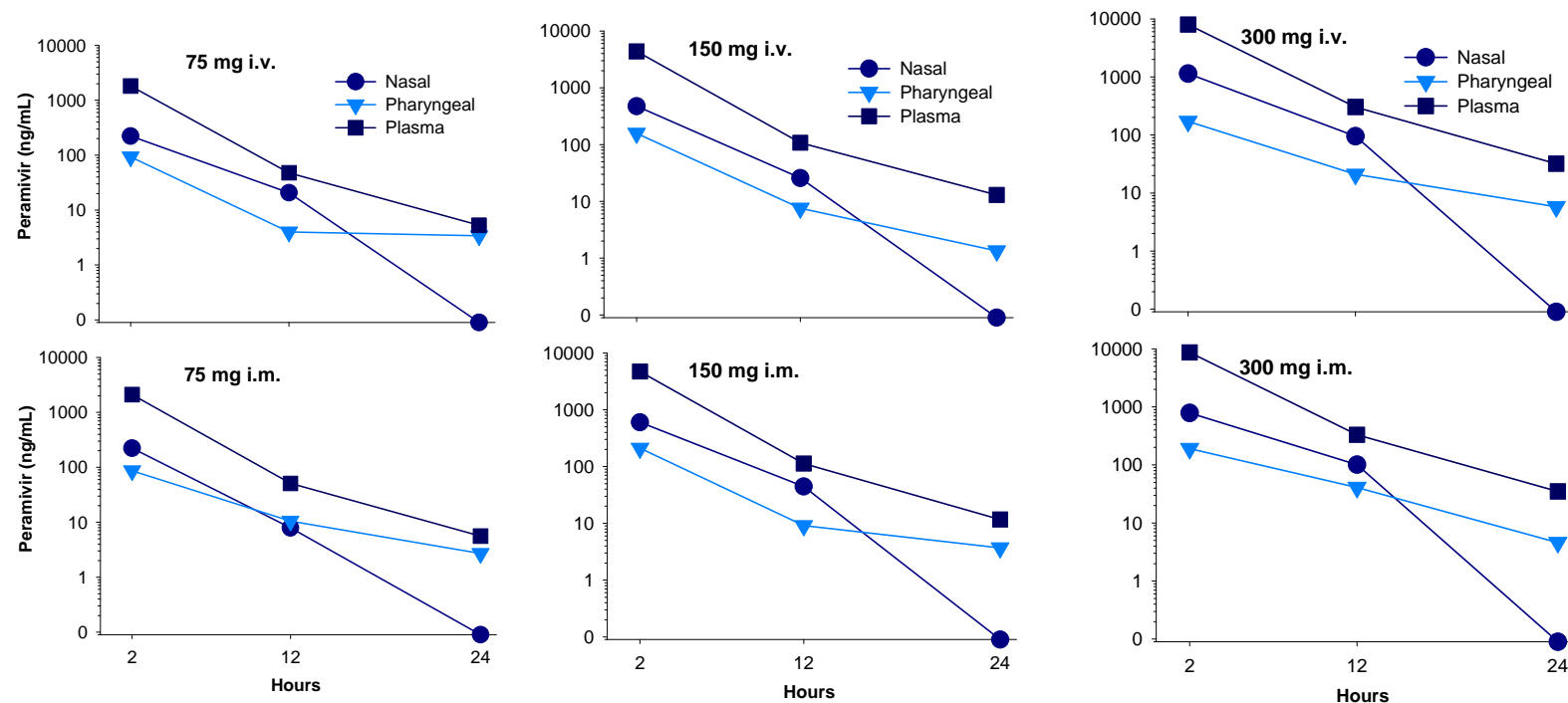
Peramivir is a novel and potent antiviral agent that inhibits influenza neuraminidase and is undergoing clinical evaluation for treatment of acute uncomplicated influenza as well as illness in hospitalized subjects. The pharmacodynamic and pharmacokinetic properties of parenterally administered peramivir, notably (1) prolonged binding to neuraminidase¹, rapid achievement of relatively high levels of drug², and (3) terminal plasma half-life of approximately 24 hours², make the drug attractive for use in treatment. Rapidly achieving high inhibitory concentrations at the sites of influenza virus replication may be important in control of the infection and in preventing emergence of viral resistance. In order to provide data that would further support dosing regimens undergoing clinical evaluation, concentrations of peramivir in nasal wash and pharyngeal gargle samples were measured at 2, 12, and 24 hours following single doses administered by both intravenous (i.v.) and intramuscular (i.m.) routes.

Materials and Methods

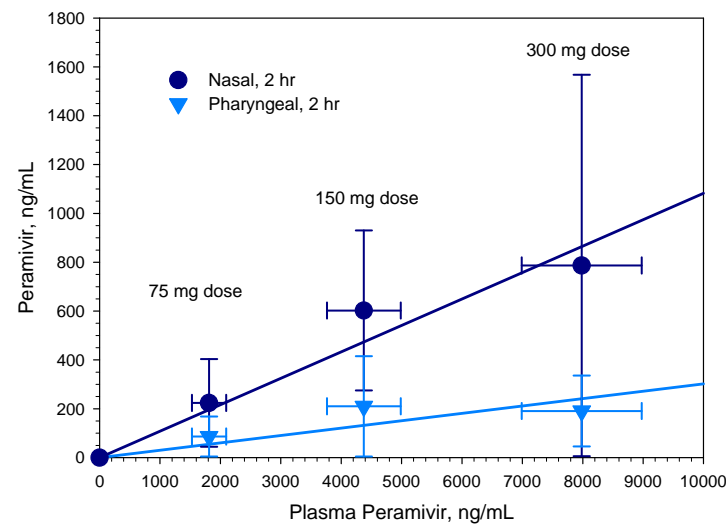
A single-center, crossover, uncontrolled, open-label study was conducted (Study BCX1812-103). Twenty-seven healthy males (85%) and females (15%) age 19-57 years participated. Full pharmacokinetic profiles for peramivir concentrations in plasma were determined. At 2, 12, and 24 hours following dosing, all subjects underwent sampling of nasal and pharyngeal secretions by means, respectively, of nasal wash and pharyngeal gargle with saline solutions. Levels of peramivir were determined and concentrations in secretions were calculated by using simultaneous (time-matched) urea concentrations in the upper respiratory tract samples and blood urea nitrogen concentrations as previously described.^{3,4}

Results

Median Concentrations (ng/mL) of peramivir in nasal and pharyngeal samples, and plasma following single intravenous and intramuscular doses.



Dose proportional relationship between mean concentrations (ng/mL) of peramivir in nasal and pharyngeal samples, and plasma 2-hours post intramuscular administration.



Mean (\pm SD) concentrations (ng/mL) of peramivir in nasal and pharyngeal samples at 2, 12, and 24 hours post-dose.

Nasal				
Dose (mg)	Route	2 hr	12 hr	24 hr
75	i.m.	223.9 (179.37)	7.9 (4.60)	Not Detected
	i.v.	222.6 (136.56)	20.7 (10.42)	
150	i.m.	602.4 (327.57)	44.5 (22.77)	Not Detected
	i.v.	475.1 (367.72)	25.9 (14.83)	
300	i.m.	786.8 (780.91)	101.7 (48.50)	Not Detected
	i.v.	1139.5 (1106.28)	95.4 (94.90)	
Pharyngeal				
75	i.m.	86.6 (82.06)	26.6 (67.61)	3.6 (1.77)
	i.v.	93.0 (107.69)	4.0 (2.18)	3.4 (2.04)
150	i.m.	210.1 (205.24)	7.3 (5.95)	2.8 (1.44)
	i.v.	158.2 (85.88)	6.4 (2.19)	2.5 (1.87)
300	i.m.	191.3 (145.01)	41.0 (58.84)	4.6 (2.20)
	i.v.	171.2 (99.97)	21.0 (32.45)	5.1 (3.99)

Conclusions

This study demonstrates that concentrations of peramivir which should exceed the IC₅₀ values for most strains of influenza A and B (viral susceptibility data not shown) are present in the upper respiratory tract for up to 24 hours following single parenteral (i.v. or i.m.) doses of peramivir. Such concentrations should produce sustained inhibition of influenza viral replication over this period. Clinical correlation of these findings should be provided by the results of ongoing trials in naturally occurring influenza infection.

References

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