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Key words
naloxone – targin – bioavailability – pharmacokinetics – oxycodone

Abstract. Objective: To determine the absolute bioavailability of naloxone from oral doses ranging from 5 mg to 120 mg. Materials and methods: In this open-label study, 28 healthy subjects received naloxone 1 mg (0.4 mg/ml) as an intravenous infusion (reference treatment), and the following oral doses as prolonged release (PR) naloxone tablets: 5 mg, 20 mg, 40 mg, 80 mg and 120 mg. The pharmacokinetic characteristics of 40 mg administered per rectum were also investigated. Each subject received five of the seven treatments as single doses with a 7 day washout between doses. Pharmacokinetic blood sampling and safety monitoring were performed for 24 h after the intravenous dose, and 72 h after the oral and rectal doses. Results: The mean absolute bioavailability of naloxone from the orally administered PR tablets was very low, ranging from 0.9% for the 5 mg dose to 2% for the 40, 80 and 120 mg doses, based on AUC_t values. The pharmacokinetics of naloxone were linear across the range of oral doses. Where AUC_{inf} values were calculated, these confirmed the results based on AUC_t values (mean absolute bioavailability ranging from 1.9% to 2.2% for the 20 mg to 120 mg oral doses). The absolute bioavailability of naloxone was higher following rectal administration compared with oral administration, but was still low at 15%. Conclusions: The mean oral absolute bioavailability of naloxone in this study was $\leq$ 2% at doses ranging from 5 mg to 120 mg.

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Introduction

Oxycodone is a World Health Organization (WHO) step III opioid analgesic used as a mainstay in the treatment of moderate to severe pain. The presence of μ-opioid receptors in the intestinal wall means that oxycodone, like all other opioid agonists, is associated with opioid-induced bowel dysfunction (OIBD). In contrast to other side-effects, OIBD does not diminish with time, and constipation is the primary symptom. The burden of OIBD often results in insufficient pain therapy in many patients, and therefore should be managed pro-actively.

A novel analgesic has been developed which combines oxycodone, a strong opioid agonist, and naloxone, an opioid antagonist, in a prolonged release (PR) tablet form [1, 2, 3]. When administered intravenously, naloxone acts centrally as a specific antidote for opiate or opioid intoxication. When administered orally in tablet form, naloxone acts locally at the μ-receptors in the gut where it has a much higher affinity than the agonist, oxycodone [1]. Consequently, the constipating effect of oxycodone is significantly reduced [4]. Thus far it has been understood that, at low doses, the first pass metabolism of naloxone in the liver is high [5]. In a previous study, naloxone was administered intravenously and orally on separate occasions to one healthy male subject. Low concentrations of naloxone were recorded following oral administration, suggesting a high first-pass metabolism [6]. Goodman and Gilman reported the mean half-life of naloxone as 1.1 h [7]. Systemic exposure is therefore expected to be negligible and insufficient to inhibit the central, pain-relieving action of oxycodone [8, 9]. Oxycodone/naloxone tablets (Targin®, Targinact®, Targiniq®) are indicated for the treatment of severe pain that can be adequately managed only with opioid analgesics. The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut.

Materials and methods

Study design

This was an open-label, single-centre, single-dose, 7-treatment, 5-period, randomized incomplete crossover study. The protocol for this study was approved by the Office for Research Ethics Committee Northern Ireland (ORECNI). The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guideline [10], the Declaration of Helsinki [11], and applicable regulatory requirements.

28 healthy men and women, aged 18 – 55 years, gave their written informed consent to participate and were enrolled into the study. Female subjects had to use a highly effective method of contraception throughout the study. Subjects were excluded from participation if they had evidence of any clinically relevant medical condition or had used opioid-containing medication within 30 days before the start of the study. The use of any prescription or non-prescription drug (excluding acetaminophen/paracetamol), vitamins, herbal and/or mineral supplements, and drugs of abuse were prohibited throughout the study. Caffeine and xanthine containing beverages were prohibited from 48 h before each dose and while resident in the study unit, and alcohol was prohibited from 48 h before until 72 h after each dose.

Subjects were randomized to receive five of the following seven single doses of naloxone with at least a 7 day washout period between each dose: 1 mg (0.4 mg/ml) administered over 30 min as an intravenous (i.v.) infusion (reference treatment), orally administered prolonged release tablets 5 mg, 20 mg (2 × 10 mg tablets), 40 mg, 80 mg (2 × 40 mg tablets) and 120 mg (3 × 40 mg tablets), and a rectally administered 40 mg prolonged

Subjects fasted from food from 8 h before until 4 h after dosing in each study period. Subjects also had restricted fluid (240 ml water at the time of dosing) from 1 hour before until 1 hour after each dose. A low-fat lunch (< 30% fat), dinner and an evening snack were provided at 4, 10 and 14 h post-dose, respectively. Menus were standardized while subjects were resident in the study unit and were the same for each study period. Subjects remained resident in the study unit until 36 h post-dose, and returned to the study unit for 48 and 72-h post-dose procedures following the oral and rectal doses. Subjects also underwent clinical evaluations within 21 days before the first dose and 3 – 7 days after the last dose.

Pharmacokinetic methods

Blood samples (6 ml) were drawn from a forearm vein into tubes containing potassium ethylenediaminetetraacetic acid pre-dose and at 15, 30, 32, 35, 40 and 45 min and 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h post-dose for the i.v. dose, and pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 9, 12, 16, 24, 32, 36, 48 and 72 h post-dose for all oral and rectal doses. Samples were centrifuged within 30 min of collection at 1,500 *g* for 15 min at 4 °C and the plasma frozen in polypropylene tubes at –20 °C within 1 hour of sampling.

Naloxone was extracted from plasma by liquid-liquid extraction. Samples were analyzed using a validated bioanalytical assay employing liquid chromatography and electrospray ionization with tandem mass spectrometric detection. The precision of the assay was within 8% and accuracy within 5% over an extended quality control concentration range of 30 – 4,000 pg/ml. The quality control samples were initially at concentrations of 30, 450 and 850 pg/ml, however many sample

Table 1. Summary statistics for naloxone pharmacokinetic parameters following intravenous infusion and prolonged release tablets.

Pharmacokinetic parameter	Statistics	Dose					
		5 mg oral	20 mg oral	40 mg oral	80 mg oral	120 mg oral	4(
AUC_t (pg.h/ml)	n	19	20	19	20	20	
	Geometric mean	158.2	1,331.1	2,868.2	5,983.5	8,939.8	
	Geometric SE	1.43	1.12	1.09	1.11	1.10	
	Exponentiated LS mean	162.1	1,351.6	2,935.8	6,137.3	8,892.1	
	Min; max	2.6; 1,161.5	613.4; 3,705.4	1,839.4; 7,131.8	2,737.0; 15,831.6	5,415.8; 36,641.9	6,564
AUC_{inf} (pg.h/ml)	n	0	5	11	15	17	
	Geometric mean	–	1,812.8	3,095.6	5,898.3	9,304.7	
	Geometric SE	–	1.12	1.11	1.12	1.10	
	Exponentiated LS mean	–	1,732.5	3,227.3	5,938.7	9,488.2	
	Min; max	–	1,409.8; 2,600.8	2,006.7; 6,110.9	2,920.9; 14,185.1	6,634.8; 36,907	8,294
C_{max} (pg/ml)	n	19	20	19	20	20	
	Geometric mean	32.45	98.57	204.69	406.59	632.98	
	Geometric SE	1.224	1.131	1.095	1.112	1.118	
	Exponentiated LS mean	33.15	102.25	204.64	413.82	639.09	
	Min; max	10.5; 343	43.4; 292	129; 594	203; 1,010	356; 2,480	75
t_{max} (h)	n	19	20	19	20	20	
	Median	5	5	5	5	1.75	
	Min; max	0.5; 16	0.5; 36	0.5; 16	0.5; 16	0.5; 16	
$t_{1/2}$ (h)	n	1	9	12	15	17	
	Mean	8.04	16.60	14.83	11.29	12.40	
	SE	–	3.160	3.502	1.137	1.150	
	LS mean	7.32	16.30	14.79	11.05	12.24	
	Min; max	8.04; 8.04	8.36; 40.19	5.59; 51.17	6.82; 20.97	5.57; 23.34	1.
LambdaZ (h^{-1})	n	1	9	12	15	17	
	Mean	0.086	0.050	0.064	0.070	0.065	
	SE	–	0.0065	0.0087	0.0061	0.0064	
	LS mean	0.098	0.041	0.054	0.076	0.064	
	Min; max	0.086; 0.086	0.017; 0.083	0.014; 0.124	0.033; 0.102	0.030; 0.124	0.(

SE = standard error; LS mean = least squares mean.

AUC_{inf}	5 mg oral vs. 1 mg i.v. infusion	–	–
	20 mg oral vs. 1 mg i.v. infusion	2.2	1.4; 3.3
	40 mg oral vs. 1 mg i.v. infusion	2.0	1.5; 2.8
	80 mg oral vs. 1 mg i.v. infusion	1.9	1.4; 2.5
	120 mg oral vs. 1 mg i.v. infusion	2.0	1.5; 2.6
	40 mg rectal vs. 1 mg i.v. infusion	15.8	11.9; 20.9
C_{max}	5 mg oral vs. 1 mg i.v. infusion	0.2	0.1; 0.3
	20 mg oral vs. 1 mg i.v. infusion	0.2	0.1; 0.2
	40 mg oral vs. 1 mg i.v. infusion	0.2	0.1; 0.2
	80 mg oral vs. 1 mg i.v. infusion	0.2	0.1; 0.2
	120 mg oral vs. 1 mg i.v. infusion	0.2	0.1; 0.2
	40 mg rectal vs. 1 mg i.v. infusion	2.0	1.5; 2.6

[a]Dose-adjusted. [b]Estimate from mixed-effects linear model. Natural log parameter estimates calculated by transforming the log-scale estimates back to the linear scale, that is estimates of ratios. [c]90% confidence intervals obtained by transforming the confidence intervals on the log-scale to the ratio scale.

concentrations were above the upper limit of quantitation, therefore two additional quality control samples were added at concentrations of 2,000 and 4,000 pg/ml. Similarly, the calibration range was extended from 10 – 1,000 pg/ml to 10 – 5,000 pg/ml. Specificity testing showed that there was no interference from a range of analytes in the chromatographic regions of interest for naloxone.

Pharmacokinetic parameters for naloxone were calculated using the WinNonlin Enterprise Edition version 4.1 software (Pharsight Corporation, St. Louis, MO, USA). From each individual plasma profile, the area under the plasma concentration-time curve measured from the time of dosing to the last measurable concentration (AUC_t) was calculated using the linear trapezoidal method. The maximum observed plasma concentration (C_{max}) and time of the maximum observed plasma concentration (t_{max}) were directly observed from the concentration-time curve. The terminal phase rate constant (LambdaZ) was estimated using those points determined to be in the terminal log-linear phase. The terminal phase half-life ($t_{1/2}$) was determined from the ratio of ln 2 to LambdaZ. The area under the plasma concentration-time curve

Safety assessments

Adverse events were recorded throughout the study, including details of severity and relationship to study medication. Vital signs (supine blood pressure, pulse rate and respiration rate) were measured and electrocardiograms (ECGs) were recorded at intervals throughout the study. Hematology, blood chemistry and urinalysis assessments were performed at the first and last study visits.

Statistical methods

Log transformed data of the AUC_t, AUC_{inf} (if available) and C_{max} for naloxone were modeled using a mixed effect linear model, with fixed terms for treatment, log(dose), period and sequence. The term "log(dose)" refers to the natural log. Treatment ratios/differences and their associated 90% confidence intervals were calculated from the least square means. The primary comparisons of interest were each of the oral tablet doses versus the i.v. infusion. A secondary comparison of interest was the rectal tablet administration versus the i.v. infusion. All reported contrasts between treatments (Table 2) were scaled by the ratio of the doses in the treatments under consideration as a form of dose-adjustment to aid the interpretation of the results.

In the subset of oral administered treatments, log transformed data of the AUC_t, AUC_{inf} (if available) and C_{max} for naloxone were modeled using a mixed effect linear model, with a linear term for log(dose) with fixed terms for period and sequence, and a correlated error-structure, otherwise referred to as a power model. The estimated coefficient for log (dose) was compared to the

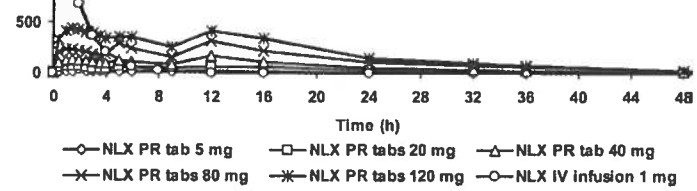

Figure 1. Mean naloxone (NLX) plasma concentration-time profiles: oral and intravenous doses.

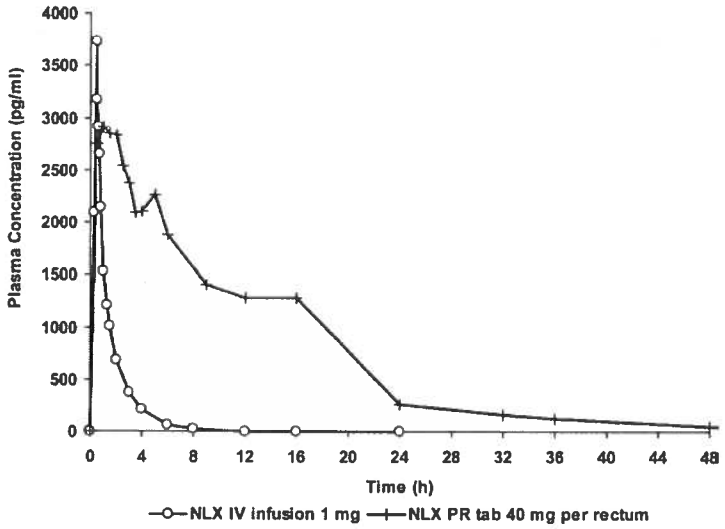

Figure 2. Mean naloxone (NLX) plasma concentration-time profiles: rectal and intravenous doses.

Table 3. Statistical results of log transformed naloxone pharmacokinetic parameters regressed on log (dose).

Parameter	Coefficient*	Effect (SE)	90% confidence interval
AUC_t	Intercept	3.56 (0.269)	3.10; 4.02
	Log dose	1.26 (0.057)	1.17; 1.35
AUC_{inf}	Intercept	4.35 (0.315)	3.81; 4.89
	Log dose	1.00 (0.061)	0.89; 1.11
C_{max}	Intercept	2.10 (0.184)	1.79; 2.42
	Log dose	0.95 (0.037)	0.88; 1.01

*Estimates from mixed-effects linear model. SE: standard error.

reference value of 1 as a global test of dose-proportionality.

This was a pharmacokinetic study that was designed to have an overall power of more than 90% to demonstrate dose-proportionality of naloxone 10/5 mg and 40/20 mg, which showed within-subject SDs on the log-scale of 0.163 – 0.192 for AUC and C_{max} of naloxone-3-glucuronide.

Statistical programming and analyses were performed using SAS® version 9.1 software (SAS Institute Inc., Cary, NC, USA).

Results

Subject disposition

28 subjects were randomized into the study; 27 of these subjects completed all five study periods. One subject withdrew due to subject choice and did not receive the 5 mg and 40 mg oral tablet doses. A total of 19 or 20 subjects received each study treatment. The study population comprised 9 female and 19 male subjects, with a mean age of 31 years (range 21 – 53 years), mean weight of 72.5 kg (range 55 – 96 kg) and a mean body mass index of 24.5 (range 20 – 28.5). Two female subjects and one male subject were Black; all other subjects were Caucasian.

Pharmacokinetic results

The mean observed plasma concentration-time profiles for naloxone are shown in Figures 1 and 2. The mean absolute bioavailability of naloxone from the orally administered PR tablets, based on the dose-adjusted AUC_t values, ranged from 0.9% for the 5 mg dose to 2.0% for the 40, 80 and 120 mg doses (Tables 1 and 2). The pharmacokinetics of naloxone were linear across the range of oral doses, confirmed by linear regression of the log(pharmacokinetic parameter) against log(dose); the 90% confi-

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