Population Pharmacokinetics of Intravenous, Intramuscular, and Intranasal Naloxone in Human Volunteers

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Abstract: To investigate the pharmacokinetics of naloxone in healthy volunteers, we undertook an open-label crossover study in which six male volunteers received naloxone on five occasions: intravenous (0.8 mg), intramuscular (0.8 mg), intranasal (0.8 mg), intravenous (2 mg), and intranasal (2 mg). Samples were collected for 4 hours after administration for 128 samples in total. A population pharmacokinetic analysis was undertaken using NONMEM. The data were best described by a three-compartment model with first-order absorption for intramuscular and intranasal administration, between-subject variability on clearance and central volume, lean body weight on clearance, and weight on central volume. Relative bioavailability of intramuscular and intranasal naloxone was 36% and 4%, respectively. The final parameter estimates were clearance, 91 L/hr; central volume, 2.87 L; first peripheral compartment volume, 1.49 L, second peripheral compartment volume, 33.6 L; first intercompartmental clearance, 5.66 L/hr; second intercompartmental clearance, 29.8 L/hr; Ka (intramuscular), 0.65; and Ka (intranasal), 1.52. Median time to peak concentration for intramuscular naloxone was 12 minutes and for intranasal, 6 to 9 minutes. A combination of intravenous and intramuscular naloxone provided immediate high and then detectable concentrations for 4 hours. Intranasal naloxone had poor bioavailability compared with intramuscular. Combined intravenous and intramuscular administration may be a useful alternative to naloxone infusions.

Key Words: naloxone, pharmacokinetics, population pharmacokinetics, therapeutic drug monitoring

(*Ther Drug Monit* 2008;30:490–496)

INTRODUCTION

Naloxone is an important drug in the treatment of opioid toxicity both in the prehospital and hospital setting. Patients with opioid poisoning requiring naloxone therapy are often difficult to cannulate as a result of previous intravenous substance abuse. This may delay the administration of antidote therapy. Intravenous drug abusers are also at increased risk of carrying bloodborne infections that could be transmitted to healthcare workers through needlestick injuries.[1] The half-life of naloxone is significantly shorter than most of the opioid agents, so its duration of action is shorter than that of most opioid agents. Patients may awaken from opioid toxicity and want to remove themselves from medical care when there is the risk of recurrence of opioid toxicity after the effects of naloxone wear off. This is a particular concern with long-acting opioids such as methadone and has prompted the use of a combination of intravenous and intramuscular naloxone in the field to prolong its duration of action. However, this approach is not evidence-based or based on an understanding of the pharmacokinetics of naloxone.

The intranasal route of administration has been shown to be clinically effective for a number of medications, including analgesics and sedatives.[2,3] Recent clinical observational studies have suggested that intranasal naloxone may be safely administered for the reversal of opioid intoxication in the prehospital and hospital settings.[4–10]

Despite naloxone being used for over 40 years, there are limited pharmacokinetic data in animals and humans.[11–16] Naloxone disappears rapidly from the serum in the initial distribution phase, over a period of approximately 15 to 20 minutes, and then has an elimination half-life ranging from 30 to 90 minutes based on a two-compartment model or estimation of the slope of the terminal portion of the concentration time curve.[11,14,16] Animal studies have been used to delineate the pharmacokinetics of naloxone through the intranasal route in rats.[17] However, there are no data describing the pharmacokinetics of intranasal naloxone in humans.

This study aimed to determine the pharmacokinetics of intranasal naloxone in humans and compare these with the pharmacokinetics of equivalent doses of naloxone delivered through the intramuscular and intravenous routes.

METHODS

This was an open-label crossover volunteer study of the pharmacokinetics of intravenous, intramuscular, and intranasal naloxone. Ethics approval was obtained from the South

Received for publication January 17, 2007; accepted May 23, 2008.
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G.K.I. is funded by an NHMRC Clinical Career Development Award ID300785.

Eastern Area Health Service Ethics Committee as well as the University of New South Wales Ethics Secretariat. Informed consent was obtained from all volunteers. In addition, the Therapeutic Goods Administration was notified.

Patient Data

Six healthy male volunteers were recruited with a median age of 25 years (range, 24–45 years), median weight of 80 kg (range, 75–100 kg), and median height of 1.78 m (range, 1.75–1.93 m). Exclusion criteria were previous or current opioid dependence or abuse, current use of opioid analgesics for pain relief, cardiorespiratory disease, current or recent upper respiratory tract infection, or abnormal nasal anatomy. Naloxone administration at the doses used in this study has not been shown to result in any adverse reactions in healthy volunteers.[18–26] The study was undertaken in a critical care setting with resuscitation facilities available in the unlikely event of an adverse drug reaction to naloxone. All patients had a cannula inserted for administration of intravenous naloxone and collection of blood for drug analysis.

Naloxone was purchased from Mayne Pharma Ltd., Melbourne, Australia, at a concentration of 400 μg/mL. Intravenous naloxone was administered through the cannula and flushed with a 5-mL bolus of saline. Intramuscular naloxone was administered with a 23-g needle as a single injection in the gluteus maximus muscle. Intranasal naloxone was administered through a Mucosal Atomiser Device (Wolf-Tory Medical, Salt Lake City, UT) with the patient lying at 45° and instructed not to swallow and breathe through the mouth for at least 1 minute. This technique was used after a trial of administration with normal saline in both the seated and supine positions revealed a significant amount of solution either lost out the nose or swallowed by the subjects. Half the volume was administered to each of the subject's nostrils.

The study was divided into five separate arms: 1) 0.8 mg intravenous (IV) naloxone; 2) 0.8mg intramuscular (IM) naloxone; 3) 0.8 mg intranasal (IN) naloxone; 4) 2 mg intravenous naloxone; and 5) 2 mg intranasal naloxone. An intramuscular injection of 2 mg was considered to be too large a volume to be administered by this route for a volunteer study so it was not included. All the subjects followed the same schedule in the previously mentioned order. There was a minimum 2-day washout period between doses of naloxone. After each administration of naloxone, blood was collected through the intravenous cannula into EDTA tubes at 5, 10, 15, 30, 45, 60, 90, 120, 180, and 240 minutes after naloxone administration for a total of 10 samples per subject in each arm. Before any blood samples were taken, 5 mL of blood was drawn from the cannula and discarded. After collection, the blood was immediately centrifuged and the plasma frozen at –20°C. All samples were assayed using high-performance liquid chromatography.[27–29] The limit of detection for the assay was 0.3 μg/L and the limit of quantification (LOQ) was 1 μg/L. The intra- and interday coefficients of variation were 11.2% at 5 μg/L; 5.2% and 6.8%, respectively, at 12 μg/L; and 7.8% and 6.2% at 40 μg/L.[28]

Data Analysis

Pharmacokinetic analysis was undertaken using NONMEM version 6.1.0 using the first-order conditional estimation method for estimation with a G77 Compiler and enabled with Wings for NONMEM Version (6.13). Postprocessing analysis of data from NONMEM output was performed with Mathematica Version 5.1.1 (Wolfram Research, Inc., Champaign, IL). There were concentration measurements below the LOQ for all subjects and administration routes. Because of the assay error associated with values between the limit of detection and LOQ, we only included values above the LOQ. However, the first concentration below the LOQ was set to 0.5 μg/L (LOQ/2) as described previously.[30] This has been shown to reduce bias dramatically in the estimated parameters within the population pharmacokinetic model, especially clearance.

One-, two-, and three-compartment models were assessed to decide the best structural model. The three-compartment model was parameterized as clearance (CL), central volume (V2), first peripheral compartment volume (V3), first intercompartmental clearance (Q3), second peripheral compartment volume (V4), and second inter-compartmental clearance (Q4). For the residual unexplained variability additive, proportional and combined error models were evaluated. Subsequently, data for IV, IM, and IN were then combined and modeled simultaneously. For the IM and IN dosing route, both first- and zero-order inputs were considered. To assess the relative bioavailability among IV, IM, and IN, the bioavailability was fixed to 1 for the intravenous route and the bioavailability estimated for IM and IN. Between-subject variability (BSV) was assumed to have a log-normal distribution and was added sequentially to the model.

Model selection decisions were based on a number of different criteria, including a reduction in the objective function value produced by NONMEM (greater than 3.8 for $P < 0.05$), plots of predicted concentrations, weighted residuals, and visual predictive plots generated from simulations. Visual predictive check plots were obtained by simulating 1000 patients each with the four occasions during which data were obtained (0.8 mg IV, 2 mg IV, 0.8 mg IM, and 2 mg IN) and then plotting the median and 90% percentile range.

Between-occasion variability (intraindividual variability) was not included in the modeling process because each occasion represented a different dose or route of administration. This meant that CL, V2, V3, V4, Q3, and Q4 were the same in each individual for each occasion allowing the estimation of the input processes. BSV was only estimated for the compartmental parameters, except BSV on input parameters for intramuscular administration in which there were more data available to estimate this parameter more accurately.

The influence of covariates was evaluated initially by visual inspection of plots of the covariates, post hoc estimated parameters, and a reduction of BSV and consideration of biologic plausibility. Weight and height were available for each subject so the influence of weight and lean body mass (LBW_{2005}) (calculated using the method suggested by Janmahasatian et al[31]) was evaluated.

Simulations

To compare a common range of intravenous dosing schedules with IM and IN naloxone, the final model was used to simulate 1000 males with a weight of 70 kg from the typical

parameter values, including BSV, for each of the following dosing schedules: 1) 0.4 mg, 0.8 mg, and 2 mg boluses of IV naloxone; 2) 0.8 mg, 1.6 mg, and 2.4 mg IM doses; and 3) 2 mg, 4 mg, and 6 mg IN doses of naloxone. Concentration versus time plots were constructed for each of these scenarios with median (50% percentile) concentrations. Time to peak concentration and peak concentration were determined for IM and IN administration.

A second set of simulations was undertaken to compare a previously recommended IV bolus and IV naloxone infusion protocol[16] with a combination of IV and IM naloxone. Again, the final model was used to simulate 1000 males with a weight of 70 kg given 1) 0.4 mg IV naloxone with an infusion at 0.25 mg/hr and a second bolus of 0.2g after 15 minutes; 2) 0.4 mg IV naloxone and 1.2 mg IM naloxone; 3) 0.4 mg IV naloxone and 1.2 mg IM naloxone delayed by 10 minutes; or 4) 0.4 mg IV naloxone, 1.2 mg IM naloxone, and a second 1.2 mg IM naloxone after 2 hours. Further simulations were undertaken with increasing doses as described by Goldfrank et al[16] and IV/IM combinations to compare for larger bolus doses.

RESULTS

All six subjects completed five arms of the study and no adverse events occurred. Naloxone was only detectable above the LOQ in two subjects after the administration of 2 mg naloxone intranasally and not detectable above the LOQ in any patient receiving 0.8 mg, so only four occasions were available for analysis. One subject was removed from the IV 0.8-mg dose because of a drug administration error, which resulted in a spurious concentration–time profile. Thus, the final data set consisted of six patients (five occurrences with 0.8 mg IV, six occurrences with 2 mg IV, six occurrences with 0.8 mg IM, and two occurrences with 2 mg IN) with 128 concentration measurements (82 after IV administration, 39 IM, and seven IN).

A three-compartment model with first-order input for IN and IM and a combined error model with a small fixed additive error model was found to best describe the data. BSV on CL and V2 (central volume) were included in the model. Addition of BSV on V3, V4, Q3, or Q4 did not reduce the objective function significantly or provided improbable estimates of BSV. The addition of BSV on absorption rate constant (Ka) for IM administration again did not provide a significant reduction in objective function value nor improve the model diagnostics.

All patients were male so sex was not included. Visual inspection of CL and V2 versus weight and LBW_{2005} plots indicated an influence on both parameters. Covariates were evaluated in the model by including a modifying effect on the CL and V2. Weight and LBW were scaled with power functions such that:

$$CL = \theta_1 \times [\frac{WT}{WT_{70}}]^{0.75};\ V_2 = \theta_2 \times [\frac{WT}{WT_{70}}]$$

The addition of weight and LBW_{2005} to CL on the model significantly reduced the objective function (ΔOBJ = –4.136). The final model included WT on V2 and LBW_{2005} on CL.

The final covariate model was a three-compartment model with first-order absorption for IM and IN administration, BSV on CL and V2, LBW_{2005} on CL allometrically scaled, and weight on V2.

$$CL = TVCL * (LBW_{2005}/70)\text{^}0.75 * EXP(ETA[1])$$

$$V2 = TVV2 * (WT/70) * EXP(ETA[2])$$

Plots of observed versus predicted concentrations and weight residuals versus predicted concentration demonstrated a good fit for the model (Fig. 1). In the WRES plot, most points appear to be normally distributed and centered around zero and most within three standard deviations. There were a couple of outliers that could not be explained or excluded. The typical population estimates and individual predicted values for the parameters are listed in Table 1. The relative bioavailability of IM and IN naloxone was 36% and 4%, respectively.

From the final model, 1000 potential patients were simulated for each of the four arms of the study (0.8 mg and 2 mg IV, 0.8 mg IM, and 2 mg IN). A visual predictive check of the final covariate model is presented in Figure 2. This shows that the final model shows very good ability to fit the central tendency of the data, whereas the 95th and 5th percentiles describe the variability well, with approximately five samples out of 128 (total number) of samples outside these percentiles.

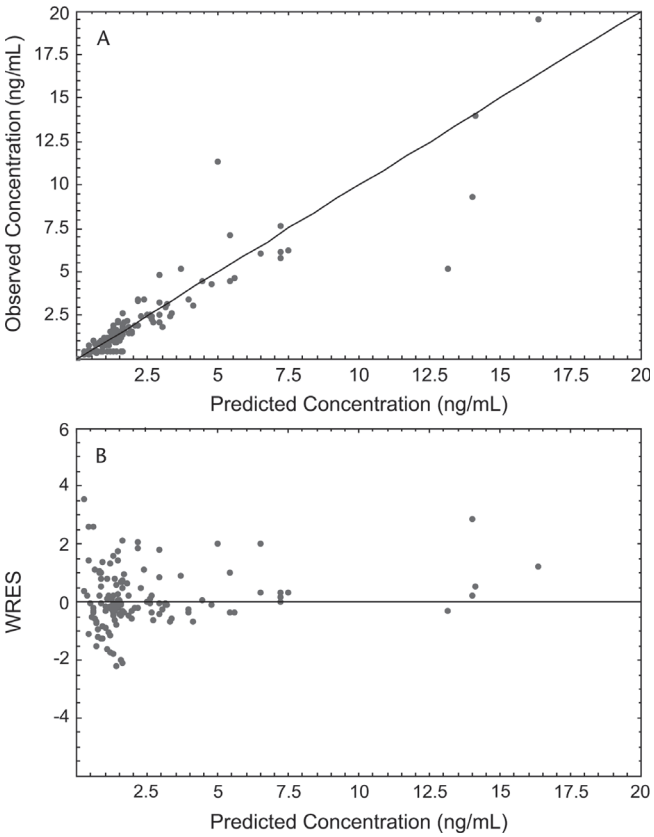

FIGURE 1. Plots of observed naloxone concentration versus posterior predicted concentrations (**A**) and weighted residuals (WRES) versus posterior predicted concentrations (**B**).

TABLE 1. Estimates for the Parameters from the Final Model and Individual Predicted Values for the Parameters.

	Mean Parameter Value	95% Percentiles*
CL (L/hr)	91	47.3–105
V2 (L)	2.87	0.75–4.8
V3 (L)	1.49	1–27.6
V4 (L)	33.6	6.7–200
Q3 (L/hr)	5.66	1.97–39.6
Q4 (L/hr)	29.8	4.82–44.3
$t_{½\alpha}$ (hours)†	0.016	—
$t_{½\beta}$ (hours)†	0.2	—
$t_{½\gamma}$ (hours)†	1.0	—
Ka[im] (hr^{-1})	0.65	0.44–0.79
Ka[in] (hr^{-1})	1.52	1.52–3.9
F_{tot}[im]	0.36	0.18–0.45
F_{tot}[in]	0.038	0.016–0.040
BSV on CL (CV%)	0.00581 (7.6%)	0–0.09
BSV on V2 (CV%)	0.25 (50%)	0.00006–0.66
Prop Err	0.101 (31.7%)	0.063–0.11
Add Err	0.001 (fixed)	

*5th and 95th percentiles obtained by 1000 nonparametric bootstraps.
†Derived parameters.
CL, clearance; V2, central volume; V3, first peripheral compartment volume; V4, second peripheral compartment volume; Q3, first intercompartmental clearance; Q4, second intercompartmental clearance; BSV, between-subject variability; CV%, percent coefficient variation; t½, half-life; Ka, absorption rate constant; im, intramuscular; in, intranasal; F_{tot}, relative fraction absorbed; Prop Err, proportional error; Add Err, additive error.

Simulations

Figure 3 shows plots for simulations of 1000 individuals for a range of IV, IM, and IN doses of naloxone. The median time to peak concentration for intramuscular naloxone ranged from 12 minutes and for intranasal from 6 to 9 minutes (Fig. 3). Figure 4 shows a comparison of the naloxone infusion nomogram suggested by Goldfrank et al[16] and the administration of simultaneous IV and IM naloxone.

DISCUSSION

This study shows that naloxone has a very poor bioavailability of 4% by the IN route and large doses that are physically impossible to administer intranasally using commercially available formulations are required to produce similar concentrations to those following IV naloxone. Intranasal absorption is rapid but does not maintain measurable concentrations for more than an hour. Therefore, the IN route is the least useful route having poor bioavailability and not maintaining concentrations. Intramuscular naloxone has a bioavailability of 35% compared with IV therapy and maintains measurable concentrations for up to 4 hours after the dose. Although there is a slight delay in peak concentration after IM naloxone compared with IN, this is only approximately 5 minutes. The combination of IV and IM naloxone provides both rapidly high and persistent plasma concentrations of naloxone. Although the concentrations are not maintained as well as an IV infusion, there are detectable concentrations for up to 4 hours, which is long enough to maintain antagonism for many opioid drugs. These results were achievable because of the simultaneous analysis of IV, IM, and IN data to provide meaningful parameter estimates. These results could not be achieved through the standard two-stage approach, and the power of the NONMEM methodology to be able to gain meaningful parameter estimates in this manner has been discussed previously.[32]

Hussain et al[17] reported the pharmacokinetics of IN naloxone at a dose of 30 μg/kg in rats. In their study, the rats had their oropharynx occluded and their nostrils glued shut after naloxone was administered to prevent any loss of the drug from the nasopharynx. Hussain found the bioavailability of IN

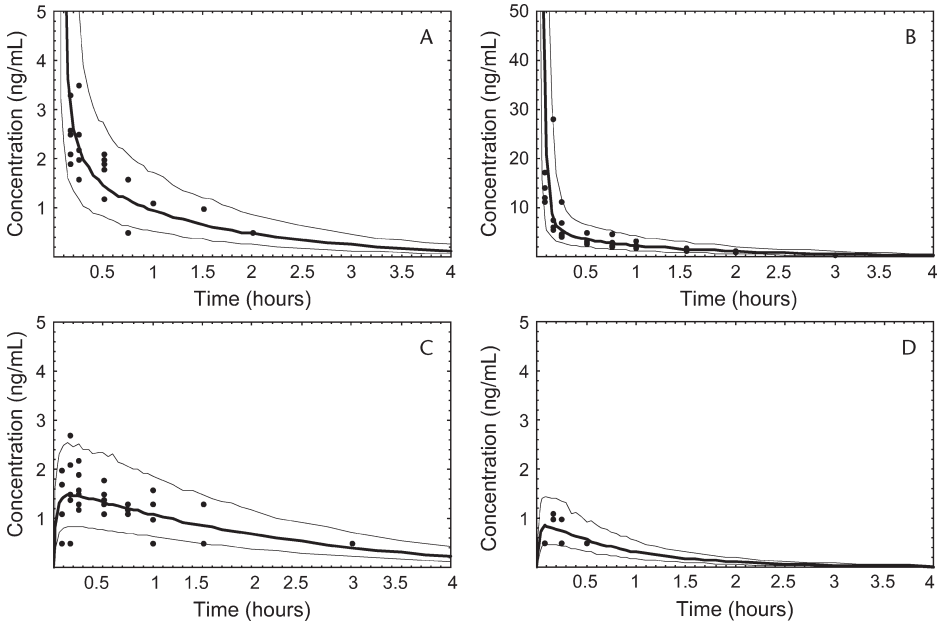

FIGURE 2. Visual predictive plots for 0.8 mg naloxone intravenously (**A**), 2 mg naloxone intravenously (**B**), 0.8 mg naloxone intramuscularly (**C**), and 2 mg naloxone intranasally (**D**). The 5th percentile, 50th percentile (median), and 95th percentile for the predicted concentrations are plotted against time and the observed data overlaid. The limit of quantitation was 1 ng/mL.

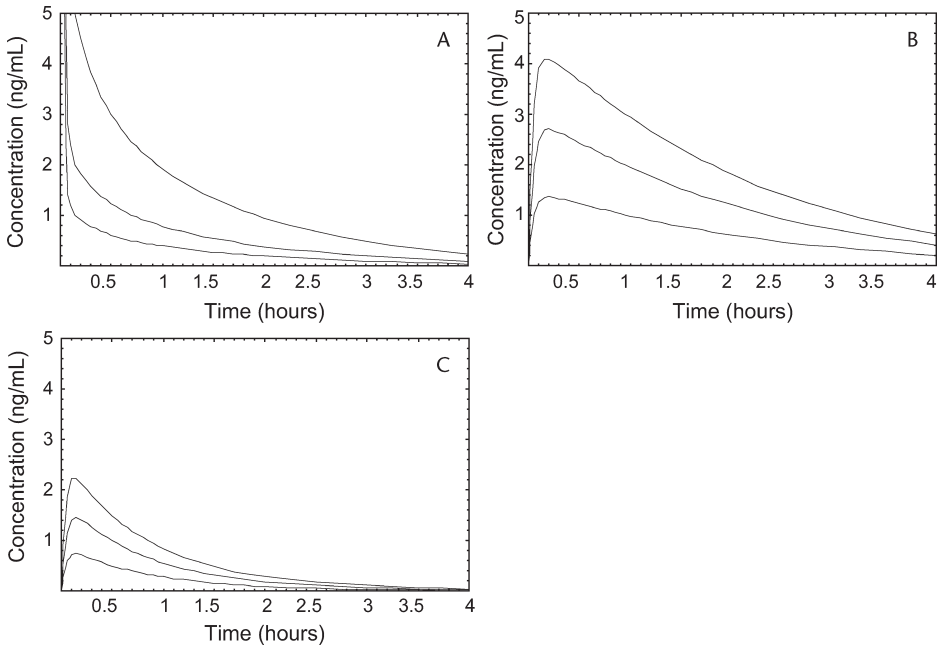

FIGURE 3. Concentration versus time plots for the 50th percentile for 1000 individuals given intravenous doses of naloxone 0.4, 0.8, and 2 mg (**A**); intramuscular doses 0.8, 1.6 and 2.4 mg (**B**); and intranasal doses 2, 4, and 6 mg (**C**).

naloxone to be equivalent to IV naloxone. The rapid absorption profile in our study suggests that the small amount absorbed was through the IN route, whereas the remainder was swallowed. It is likely in our study in which IN naloxone was administered in an unoccluded nasopharynx that the majority of the naloxone was able to be swallowed and not able to be absorbed through the nasal mucosa. A previous study has shown that the bioavailability of oral naloxone is minimal (less than 1%) resulting from extensive first pass metabolism, supporting our observations.[11,17]

There are no pharmacokinetic–pharmacodynamic studies of naloxone, making it difficult to determine the appropriate dose required to achieve a target concentration or concentration–time profile to maximize its antidote efficacy. We are aware of one study on the pharmacodynamic effects of naloxone measured by the reversal of morphine-depressed respiration.[33] This study gives an indication of the potency of naloxone and the dose of naloxone required to produce a dose ratio of morphine can be calculated. For example, to reduce the effect of 20 mg of morphine to the effect of 4 mg (dose ratio of 5) 550 μg of naloxone is required, or 1100 μg to reduce the effect to 2 mg. However, this is in normal subjects and it is difficult to interpret this in the overdose setting with other opioid agonists such as heroin or methadone and in patients with significant tolerance to opioids.

A previously developed approach to naloxone antagonism by Goldfrank et al[16] recommended dosing to be based on clinical response. The IV infusion protocol they recommended was based on the initial dose required to cause clinical reversal. We have shown that an IV and IM dose of naloxone may provide suitable antagonism for 2 hours and for another 2 hours with a repeat intramuscular dose (Fig. 4). This approach can also be based on the initial dose required to produce reversal of opioid effects by delaying the IM injection for 10 minutes, by which time the initial IV dose is established and three times this dose can be given as an IM dose (Fig. 4). The administration of IM naloxone is easier, not requiring an infusion pump. However, with long-acting opioids such as methadone, or slow-release morphine preparations, in which naloxone may be required for over 4 hours, an infusion is the safest option.

Clinical trials have demonstrated an effect of IN naloxone when administered with a Mucosal Atomiser Device.[4,8,10] Barton et al[8] studied the prehospital administration of 2 mg intranasally (concentration 1 mg/mL). In their cohort of 30 patients, 11 (37%) responded to naloxone. Ten patients required only a single dose of IN naloxone with an average response time of 3.4 minutes. Subsequent to this study, Barton et al reported a similar group of patients and found that of the 52 patients who responded to naloxone, 43 responded to IN naloxone alone.[5]

Kelly et al[9] compared 2 mg of IM and IN naloxone in patients with suspected opioid intoxication in the prehospital setting. Based on their clinical outcome, it appeared that there was a slower onset of action with IN compared with IM naloxone. This is not consistent with the pharmacokinetics of IN naloxone we have shown. However, their finding that a greater percentage of patients receiving IN naloxone required further doses to reverse sedation (13% versus 26%) is consistent with the shorter action of IN naloxone. In addition, the study showed that the IM group had a higher incidence of adverse effects, most likely as a result of precipitation of a withdrawal-like phenomenon.

It is not completely clear why the clinical trials of IN naloxone are not consistent with our study. The explanation may be that only small amounts (0.05–0.1 mg) of naloxone are sufficient to produce opioid antagonism so that even with such poor bioavailability, 2 mg of IN naloxone is sufficient to be effective. In our study, IN naloxone was administered in awake healthy volunteers who, despite best efforts, swallowed a significant percentage of the administered drug that pooled

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