The effect of age on the pharmacokinetics of the opioid antagonist nalmefene

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- 1 The disposition of nalmefene was evaluated in young and elderly normal healthy volunteers. Subjects received either a single 1 mg ($n=18$ young; $n=11$ elderly) or 2 mg ($n=8$ young; $n=15$ elderly) intravenous bolus dose of nalmefene.
- 2 Following the administration of nalmefene, the initial plasma concentrations were significantly higher in elderly *vs* young subjects. The higher concentrations were the result of the 30 to 40% smaller central compartment apparent volume of distribution that was observed in the elderly subjects as compared with the young volunteers (2.8 ± 1.1 *vs* 3.9 ± 1.1 l kg⁻¹ for 1 mg dose). The elderly volunteers also had a significantly shorter distributional half-life ($t_{1/2\lambda_1}$) than young volunteers (0.7 ± 0.7 *vs* 1.3 ± 0.8 h for 1 mg dose). No significant differences between groups were observed for the elimination half-life, clearance or steady-state apparent volume of distribution.
- 3 Although transiently higher nalmefene plasma concentrations were observed in the elderly immediately following drug administration, there was no association between this observation and adverse events. We conclude that no dosage alteration is warranted in elderly patients.

Keywords nalmefene opioid antagonists pharmacokinetics elderly

Introduction

Nalmefene HCl (REVEX[®]) is a parenterally active opioid antagonist. At doses in the range of 0.1–1 µg kg⁻¹, it has effectively reversed post-operative opioid respiratory depression without ablating the analgesic response to subsequently administered opioids [1, 2]. When administered at higher doses (0.5–1.6 mg), nalmefene has been shown to be effective in the reversal of respiratory depression in patients who presented to the emergency room with opioid overdose [3]. Naloxone was previously the only available treatment for the reversal of opioid-induced respiratory depression. However, its relatively short elimination half-life of 1–1.5 h has limited its clinical usefulness, and recurrence of respiratory depression has been reported [2, 4].

Previous investigations of the disposition of nalmefene indicate that it is primarily eliminated (up to 65%) by conjugation with glucuronic acid with subsequent elimination in the urine [5]. Although only a minimal amount (<8%) of unchanged nalmefene is eliminated

in urine, the disposition of nalmefene is significantly altered in patients with end-stage renal disease [6]. It is widely distributed with an average steady-state volume of distribution of approximately 8 l kg⁻¹, a total body clearance that approaches 1100 ml min⁻¹ and a terminal elimination half-life of approximately 10 h in healthy middle age volunteers [6]. The longer elimination half-life contributes to the observation that nalmefene has a longer duration of action than naloxone, and is more effective in reversing opioid-induced respiratory depression and sedation [2, 4].

Increasing age results in alterations of many physiological functions including cardiac index, glomerular filtration rate and hepatic metabolism [7]. Furthermore, alterations in body fat content as well as intra- and extracellular body water have been reported in elderly adults [8, 9]. These physiological changes have been associated with alterations in the pharmacokinetics of a number of medications, and in some cases a change in the expected pharmacodynamic response [10]. The purpose of this study was to characterize the pharmaco-

kinetics of nalmefene at two doses in healthy young and elderly volunteers and to assess the relationship between age and nalmefene disposition.

Methods

Twenty-six young and twenty-six elderly volunteers participated in separate protocols designed to characterize the pharmacokinetics of nalmefene at two doses in a parallel fashion. Volunteers gave written informed consent prior to participation in the studies, which were approved by the respective Institutional Review Boards. All subjects were over 18 years of age (range 19–80 years), non-smokers and healthy as confirmed by medical history, physical examination, blood chemistries and urine analysis. Creatinine clearance (CL_{cr}) was calculated as described by Cockcroft & Gault [11]. None of the subjects was receiving concomitant drug therapy.

All participants were admitted to the Research Center the evening prior to the administration of nalmefene. Subjects fasted for 8 h before and 4 h after drug administration. Volunteers received either a single 1 mg ($n=18$ young; $n=11$ elderly) or 2 mg ($n=8$ young; $n=15$ elderly) intravenous bolus dose of nalmefene free base (equivalent to 1.11 or 2.22 mg nalmefene hydrochloride and 2.7 or 5.3 μmol , respectively). Blood samples (10 ml) were drawn prior to drug administration and at 0.08, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 18, 24, 36, and 48 h after administration. Blood samples were centrifuged for 10 min and the resultant plasma placed in polypropylene tubes and stored frozen at -20°C until analysis. Safety assessments included seated blood pressure, pulse and respiratory rate, which were measured before nalmefene administration and just prior to the collection of each blood sample.

Analytical method

The concentration of nalmefene in plasma was determined by a specific radioimmunoassay (r.i.a.) as previously described by Dixon *et al.* [12]. Briefly, nalmefene was separated from the glucuronide metabolite by ether extraction at pH 9. The extract was dried down, reconstituted, and then quantitated by r.i.a. (Harris Laboratories, Lincoln, NE). Nalmefene was detected by rabbit antiserum to naltrexone-6-(carboxy methyl) oxime conjugated to bovine serum albumin. The assay was linear from the lower limit of quantitation of 0.0625 to 2 ng ml^{-1} in plasma. If necessary, samples were diluted until the measured concentration was in the appropriate range. The inter- and intraday coefficients of variation in plasma ranged from 3 to 11.3%.

Data analysis

Pharmacokinetic analysis The pharmacokinetic parameter estimates of nalmefene were determined by compart-

mental analysis. Two and three compartment pharmacokinetic models were fitted to the data by weighted ($1/y^2$) nonlinear regression analysis using PC-NONLIN (Statistical Consultants, Inc., Research Triangle Park, NC, USA). Model selection was based on the Akaike information criterion and the coefficients of variation of the parameter estimates [13, 14]. Based on these criteria, the two compartment model provided the best fit to the data. Therefore, only these parameters are presented. The pharmacokinetic parameters that were estimated include the initial and terminal disposition rate constants (λ_1 and λ_z , respectively) and y-intercepts (A and B), area under the plasma concentration-time curve to infinity (AUC), first moment of the concentration versus time curve (AUMC), and the maximum plasma concentration (C_{max}). The terminal elimination half-life ($t_{1/2\lambda_z}$) was calculated as $0.693/\lambda_z$. The central compartment apparent volume of distribution (V_c) was derived from the ratio of dose and C_{max} and the total body clearance (CL) of nalmefene was determined from the quotient of dose and AUC. The mean residence time (MRT) was calculated as AUMC/AUC and the steady-state apparent volume of distribution (V_{ss}) was calculated as the product of CL and MRT.

Statistical analysis The demographic characteristics of the elderly and young subjects were compared using analysis of variance for continuous data and Fishers exact test for categorical data. Data are presented as mean $\pm$ s.d. with 95% confidence intervals (CI) for the mean difference. The pharmacokinetic parameter estimates were assessed for normality of distribution using the Wilks-Shapiro test. Parameters that were non-normally distributed were log transformed prior to statistical comparisons. Comparisons between the young and elderly at each dose level were made using the independent *t*-test. Computations were performed using version 6.08 of Statistical Analysis Software (SAS Institute, Cary, NC, USA) and $P < 0.05$ was considered statistically significant.

Results

The demographic characteristics of the young and elderly volunteers are shown in Table 1. Based on previous investigations by our group, we determined that a sample size of eight subjects per group would be needed to detect a 35% difference in the most variable parameter (clearance) with 80% power at the 0.05 level of significance. Our sample sizes were 18 and 11 for the 1 mg dose and 8 and 15 for the 2 mg dose for young and elderly subjects, respectively. Although the optimal design would be to have equal numbers of subjects in each group, we chose to include all of the subjects that matched the criteria so that the largest number of subjects could be evaluated. Nalmefene was well tolerated after each dose in both age groups. Following intravenous administration, the decline in nalmefene plasma concentrations was best described by a two compartment model in all young and elderly volunteers

Table 1 Demographic characteristics of young and elderly volunteers (mean (s.d.))

		Age (years)	Weight (kg)	S_{cr} ($\mu\text{mol l}^{-1}$)	CL_{cr} (ml s^{-1})
Dose 1 mg					
Young	18	23.8 (4.2)	76.1 (8.3)	101.7 (8.8)	1.70 (0.17)
Elderly	11	70.7 (5.7)	71.4 (7.8)	111.4 (11.5)	0.86 (0.12)
<i>P</i> value		<0.001	NS	<0.02	<0.001
Dose 2 mg					
Young	8	28.1 (4.6)	77.7 (12)	99.9 (15.0)	1.67 (0.25)
Elderly	15	68.3 (4.3)	75.8 (10.8)	107.0 (8.8)	0.96 (0.16)
<i>P</i> value		<0.001	NS	NS	<0.001

after either the 1 mg or 2 mg dose. Figure 1 displays the mean plasma concentration-time profile following the 1 or 2 mg nalmefene bolus dose in young and elderly subjects. The pharmacokinetic parameter estimates for the 1 and 2 mg doses are summarized in Table 2. The

results for each dose were consistent and indicate that the central compartment apparent volume of distribution is 30% to 40% smaller in the elderly (1 mg dose: 3.9 ± 1.1 vs 2.8 ± 1.1 l kg^{-1} ; 95% CI of the mean difference was 0.2 to 2.0; $P < 0.05$; 2 mg dose: 3.7 ± 1.6 vs 2.2 ± 1.5 l kg^{-1} ; 95% CI of the mean difference was 0.1 to 2.9; $P < 0.05$). This difference in apparent volume/of distribution yields higher initial plasma concentrations in the elderly as compared to the young. The elderly also had a significantly shorter distributional half-life ($t_{1/2\lambda_1}$) than was observed in the young volunteers.

The total body clearance of nalmefene was similar after each dose and was not different between the young and elderly groups (Figure 2). Although the central compartment apparent volume of distribution was significantly smaller in the elderly, no difference was observed in the steady-state apparent volume of distribution, which was approximately 9.0 l kg^{-1} after the 1 mg dose and 9.2 l kg^{-1} after the 2 mg dose for both populations. The terminal elimination half-life of nalmefene was not significantly different at either dose level in the elderly and young subjects.

The concentration-time profiles of nalmefene in the

Figure 1 Nalmefene plasma concentration-time profiles following intravenous bolus administration of a) 1 mg and b) 2 mg to young ($\square$) and elderly ($\circ$) healthy volunteers. Data are the mean $\pm$ s.e. mean and the lines represent the fitted lines for the young (---) and elderly (—).

Table 2 Nalmefene pharmacokinetic parameter estimates (data are mean $\pm$ s.d.)

Parameter	Young subjects	Elderly subjects	95% CI of the mean difference	P
<i>Dose 1 mg</i>				
AUC (ng ml ⁻¹ h)	16.6 $\pm$ 4.5	17.3 $\pm$ 2.4	-3.7 to 2.3	0.47
Clearance (l h ⁻¹)	63.6 $\pm$ 14.7	58.8 $\pm$ 7.9	-5.1 to 14.7	0.47
<i>t</i> _{1/2λ_1}	1.3 $\pm$ 0.8	0.7 $\pm$ 0.7	0.0 to 1.2	0.023
<i>t</i> _{1/2λ_z}	10.8 $\pm$ 5.2	9.4 $\pm$ 4.6	-2.5 to 5.3	0.49
<i>V</i> _c (l kg ⁻¹)	3.9 $\pm$ 1.1	2.8 $\pm$ 1.1	0.2 to 2.0	0.015
<i>V</i> _{ss} (l kg ⁻¹)	8.6 $\pm$ 1.7	8.6 $\pm$ 2.5	-1.6 to 1.6	0.89
<i>Dose 2 mg</i>				
AUC (ng ml ⁻¹ h)	29.4 $\pm$ 7.4	30.6 $\pm$ 5.4	-6.8 to 4.4	0.66
Clearance (l h ⁻¹)	72.5 $\pm$ 20.1	67.4 $\pm$ 11.8	-8.6 to 18.8	0.44
<i>t</i> _{1/2λ_1}	1.2 $\pm$ 0.9	0.5 $\pm$ 0.5	0.1 to 1.3	0.026
<i>t</i> _{1/2λ_z}	9.4 $\pm$ 2.3	9.3 $\pm$ 2.2	-1.9 to 2.1	0.94
<i>V</i> _c (l kg ⁻¹)	3.7 $\pm$ 1.6	2.2 $\pm$ 1.5	0.1 to 2.9	0.029
<i>V</i> _{ss} (l kg ⁻¹)	9.1 $\pm$ 1.5	9.4 $\pm$ 1.6	-1.7 to 1.1	0.71

Figure 2 Comparison of a) central compartment apparent volume of distribution, b) steady-state apparent volume of distribution, and c) clearance of nalmefene in the young and elderly volunteers. ○ 1 mg, □ 2 mg. Data are mean (—) and 95% CI (---).

peripheral compartment were estimated in the young and elderly subjects using the mean derived pharmacokinetic parameter estimates from the 1 mg dose (which were comparable to the estimates from the

2 mg dose). The results of this simulation (Figure 3) indicate that elderly subjects would achieve higher peripheral compartment concentrations than young subjects.

Figure 3 Concentration of nalmefene in the peripheral compartment simulated from the mean compartmental parameters of the young (---) and elderly (—) volunteers following the 1 mg dose.

Discussion

Nalmefene disposition followed a biexponential decline in these elderly and young subjects with a terminal elimination $t_{1/2}$ of 9–11 h and total body clearance of 60 to 70 l h⁻¹, which was similar to previous observations by our group in healthy middle aged adults [6]. The initial plasma nalmefene concentrations in the elderly group were approximately twice those observed in the young but declined to comparable values shortly after nalmefene administration as the result of a significantly shorter distributional half-life. This transient increase in plasma concentrations was the result of a significantly smaller (30–40%) central compartment apparent volume of distribution in the elderly. No other significant differences in pharmacokinetic parameters were observed.

Several physiological factors such as vascular volume, cardiac output, distribution of blood flow to and within different organs, solubility and partitioning in rapidly equilibrating tissues, and protein binding may influence the distribution volume of a drug [7–10]. Those variables that are independently affected by age could contribute to alterations in the central compartment volume of distribution as was observed in this study. It is known that between the ages of 20 and 80 systemic vascular resistance increases while cardiac output, renal blood flow, and hepatic perfusion decrease by 30% to 40% [7, 15–17]. Changes in these variables may contribute to the smaller central compartment volume of distribution and thus higher initial plasma concentrations of some medications in the elderly.

Age-related alterations in apparent volume of distribution have been reported previously for several other compounds [18–21]. Owen *et al.* [18] evaluated the pharmacokinetics of the opioid analgesic morphine in seven elderly and 13 young healthy volunteers. They found that both the steady-state volume of distribution and central compartment distribution volume of morphine were reduced by approximately 50% in elderly as

compared with young volunteers. Arden *et al.* [20] evaluated the pharmacokinetics of etomidate, an intravenous anaesthetic agent, in 21 surgical patients ranging in age from 22 to 82 years. The steady-state volume of distribution of etomidate was not related to age, however the central distribution volume was decreased by approximately 42% in the elderly. A more substantial reduction in the central compartment volume of distribution was observed by Homer & Stanski [21] with the intravenous anaesthetic thiopentone. In that study the central volume was decreased by 90% in the elderly while the steady-state volume was unchanged. They concluded that the pharmacokinetics of thiopentone explained the earlier clinical observations of decreased initial dose requirements in the elderly to maintain the same level of anaesthesia.

It has been hypothesized that the opioid receptor may be kinetically identifiable with the peripheral compartment of the two compartment model. This was proposed to explain the delayed onset of analgesia with parenterally administered morphine. Owen *et al.* [18] using morphine pharmacokinetic data from young and elderly subjects simulated the peripheral compartment concentrations of morphine and demonstrated that the elderly would achieve higher peripheral compartment concentrations than the young subjects. This may partially explain the reported increased sensitivity of elderly subjects to the analgesic effects of morphine. If one accepts the hypothesis that the opioid analgesic receptor site is peripherally located, then modeling nalmefene concentrations in the peripheral site may provide insight into the pharmacodynamic response. We simulated the peripheral compartment concentrations using the mean two compartment pharmacokinetic parameters obtained after the 1 mg dose. The results of this simulation are shown in Figure 3. The peripheral compartment volume of distribution is 20% larger in the elderly. However, the peripheral compartment concentrations are greater in the elderly than in the young for up to 12 h due to differences in the intercompartmental rate constants. The elderly would be expected to achieve higher maximal concentrations in the peripheral compartment (1.4 vs 1.1 ng ml⁻¹) at an earlier time (1.4 vs 2.7 h) compared with the young. The clinical significance of these higher peripheral compartment concentrations cannot be determined from the present study. However, since the simulation reported by Owen and that presented here indicate that increased nalmefene peripheral concentrations would parallel those of an opiate such as morphine, the pharmacodynamic response to nalmefene may be similar in the elderly and young patients.

A potentially confounding variable in evaluating the effect of age on the disposition of nalmefene in this study is renal function. An age related decline in renal function would be expected and in this study, the estimated creatinine clearance is significantly lower in the elderly subjects than in the young subjects (Table 1). The significant difference that was observed between the elderly and young groups is also seen when the participants are grouped by renal function. This may suggest that renal function influences the V_c and that

age does not independently affect V_c . However, in a previous study by our group, both the central compartment and steady-state apparent volumes of distribution were larger in patients with end-stage renal disease than in control subjects. Furthermore, when the data from these studies are combined, there is no significant difference in V_c when subjects are grouped by renal function [6]. Thus, the smaller V_c observed in this study is most likely the result of advanced age.

In conclusion, we have demonstrated significant relationships between central compartment apparent volume of distribution and the distributional half-life of nalmefene with age. Using computer simulations, we have suggested how these alterations may affect nalmefene concentrations in the peripheral (active) compartment. However, since the transient elevations in plasma nalmefene concentrations following a 1 or 2 mg intravenous dose were not associated with any adverse events, we conclude that no changes in the dosing regimen are recommended in the elderly population.

References

- 1 Glass PS, Jhaveri RM, Smith LR. Comparison of potency and duration of action of nalmefene and naloxone. *Anesthes Anal* 1994; **78**: 536–541.
- 2 Konieczko KM, Jones JG, Barrowcliffe MP, Jordan C, Altman DG. Antagonism of morphine-induced respiratory depression with nalmefene. *Br J Anaesth* 1988; **61**: 318–323.
- 3 Kaplan JL, Marx JA. Effectiveness and safety of intravenous nalmefene for emergency department patients with suspected narcotic overdose: a pilot study. *Ann Emerg Med* 1993; **22**: 187–190.
- 4 Barsan WG, Seger D, Danzl DF, et al. Duration of antagonistic effects of nalmefene and naloxone in opiate-induced sedation for emergency department procedures. *Am J Emerg Med* 1989; **7**: 155–161.
- 5 Dixon R, Howes J, Gentile J, et al. Nalmefene: intravenous safety and kinetics of a new opioid antagonist. *Clin Pharmacol Ther* 1986; **39**: 49–53.
- 6 Matzke GR, Frye RF, Alexander A, et al. The effect of renal insufficiency and hemodialysis on the pharmacokinetics of nalmefene. *J Clin Pharmacol* 1996; **36**: 144–151.
- 7 Tsujimoto G, Hashimoto K, Hoffman BB. Pharmacokinetic and pharmacodynamic principles of drug therapy in old age. Part 1. *Int J Clin Pharmacol Ther Toxicol* 1989; **27**: 13–26.
- 8 Forbes GB, Reina JC. Adult lean body mass declines with age: some longitudinal observations. *Metabolism: Clinical & Experimental* 1970; **19**: 653–663.
- 9 Novak LP. Aging, total body potassium, fat-free mass, and cell mass in males and females between ages 18 and 85 years. *J Gerontol* 1972; **27**: 438–443.
- 10 Tsujimoto G, Hashimoto K, Hoffman BB. Pharmacokinetic and pharmacodynamic principles of drug therapy in old age. Part 2. *Int J Clin Pharmacol Ther Toxicol* 1989; **27**: 102–116.
- 11 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31–41.
- 12 Dixon R, Hsiao J, Taaffe W, Hahn E, Tuttle R. Nalmefene: radioimmunoassay for a new opioid antagonist. *J Pharm Sci* 1984; **73**: 1645–1646.
- 13 Akaike H. An information criterion (AIC). *Math Scientist* 1976; **14**: 5–9.
- 14 Yamaoka K, Nakagawa T, Uno T. Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. *J Pharmacokinet Biopharm* 1978; **6**: 165–175.
- 15 Leithe ME, Hermiller JB, Magorien RD, Unverferth DV, Leier CV. The effect of age on central and regional hemodynamics. *Gerontology* 1984; **30**: 240–246.
- 16 Massoud N. Pharmacokinetic considerations in geriatric patients. In *Pharmacokinetic Basis for Drug Treatment*. Edited by Benet, L.Z. New York, Raven Press, 1984; 282–310.
- 17 Brandfonbrenner M, Landowne M, Shock NW. Changes in cardiac output with age. *Circulation* 1955; **2**: 557–566.
- 18 Owen JA, Sitar DS, Berger L, Brownell L, Duke PC, Mitenko PA. Age-related morphine kinetics. *Clin Pharmacol Ther* 1983; **34**: 364–368.
- 19 Baillie SP, Bateman DN, Coates PE, Woodhouse KW. Age and the pharmacokinetics of morphine. *Age Ageing* 1989; **18**: 258–262.
- 20 Arden JR, Holley FO, Stanski DR. Increased sensitivity to etomidate in the elderly: initial distribution versus altered brain response. *Anesthesiology* 1986; **65**: 19–27.
- 21 Homer TD, Stanski DR. The effect of increasing age on thiopental disposition and anesthetic requirement. *Anesthesiology* 1985; **62**: 714–724.

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