# Multiple-Dose Evaluation of Intravenous Hydromorphone Pharmacokinetics in Normal Human Subjects

Harlan F. Hill, PhD, Barbara A. Coda, MD, Akira Tanaka, DDS, PhD, and Randy Schaffer, MS



HILL HF, CODA BA, TANAKA A, SCHAFFER R. Multiple-dose evaluation of intravenous hydromorphone pharmacokinetics in normal human subjects. Anesth Analg 1991;72:330–6.

*We measured the pharmacokinetics of hydromorphone in normal volunteers given three doses of the drug (10, 20, and 40 μg/kg) as intravenous 45-s injections on different days. Concentrations of hydromorphone in plasma from serial blood samples were measured by a high-performance liquid chromatography method specific for hydromorphone with a detection limit of 0.1 ng/mL. In all cases, plasma hydromorphone concentration versus time data for individual subjects were best described by a triexponential (instead of mono- or biexponential) function. Furthermore, we found that the pharmacokinetics of hydromorphone was independent of dose across the range studied. Averaged across doses, the distribution and terminal elimination half-lives were 1.27 min ($t_{1/2\pi}$), 14.7 min ($t_{1/2\alpha}$), and 184 min ($t_{1/2\beta}$), respectively. Average values for systemic clearance, initial dilution volume, and steady-state volume of distribution were 1.66 L/min (Cl), 24.4 L (Vc), and 295 L ($Vd_{ss}$). Our results indicate that hydromorphone pharmacokinetic parameters are linear across a fourfold range of doses that are usually employed clinically and that previously reported pharmacokinetic values for hydromorphone (based on radioimmunoassay measurements) deserve reconsideration.*

**Key Words:** ANALGESICS, HYDROMORPHONE—pharmacokinetics. PHARMACOKINETICS, HYDROMORPHONE.

Hydromorphone, the 6-oxo derivative of morphine, is an opioid with appreciable selectivity for μ-opioid receptors. Pharmacodynamically, hydromorphone differs from the parent drug mainly in potency. The onset and duration of clinical analgesic effect of hydromorphone and morphine are similar (1,2). Like morphine, hydromorphone is a hydrophilic opioid with an octanol/water partition coefficient of about 1 (3) although even lower values (i.e., 0.3) have been reported (4). Hydromorphone is excreted mainly as the 3-glucuronide in humans (5), and little if any hydromorphone-6-glucuronide is formed in humans.

For a drug that has been used clinically for so many years, it is surprising that the pharmacokinetics of hydromorphone has not been thoroughly studied. In the two pharmacokinetic studies that have been published, radioimmunoassays designed for measurement of morphine were employed without assurances that they were specific for hydromorphone quantitation; theoretically, hydromorphone metabolites could cross-react with the antibody. Vallner et al. (6) measured hydromorphone concentrations in plasma of patients given 2-mg bolus intravenous injections of hydromorphone. They reported that hydromorphone followed "single-compartment" pharmacokinetics, with an elimination half-life of 158 min, apparent (extrapolated) volume of distribution of 91 L, and total clearance of about 0.4 L/min. In the other study (7), hydromorphone pharmacokinetics was best described by biexponential decay curves in normal volunteers. Parab et al. (7) reported distributional and elimination half-lives of 4.2 and 142 min, respectively, total clearance of 1.02 L/min, initial dilution ("central compartment") volume of 16 L, and an apparent volume of distribution of 203 L. As is apparent, the studies differ markedly in most respects and the pharmacokinetics of hydromorphone after intravenous dosing remains unclear. Furthermore, in previous studies, blood was not sampled early enough after the bolus hydromorphone doses to characterize fully the distributional properties of the drug.

Supported by grants from the National Institute on Drug Abuse (DA 05513) and the National Cancer Institute (CA 38552), and by assistance from Abbott Laboratories.

Received from the Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, Washington; and the Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington. Accepted for publication October 31, 1990.

Address correspondence to Dr. Hill, Pain and Toxicity Research Program, Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, WA 98104.


0003-2999/91/$3.50

Hydromorphone is receiving renewed attention as an alternative to morphine for treatment of prolonged cancer-related pain (8,9). Because it can be prepared in more concentrated aqueous solutions than morphine and because it is about seven times more potent (1,10), hydromorphone is being used with increasing frequency in cancer patients who require high parenteral doses of an opioid analgesic for long-term pain control. This resurgent interest in hydromorphone has increased the importance of improving our understanding of hydromorphone pharmacokinetics in human subjects. In this report, we describe results obtained in a group of relatively young, healthy volunteers as a basis for comparison of hydromorphone pharmacokinetics in cancer patients of both similar and different ages involved in studies in progress.

We used a specific high-performance liquid chromatography method to determine the pharmacokinetics of hydromorphone at three different intravenous dose levels in a group of 10 normal volunteers in order to further define pharmacokinetic parameters of this widely used opioid and to establish whether or not its pharmacokinetics was dose-dependent. This represents the first detailed report on hydromorphone pharmacokinetics using highly specific high-performance liquid chromatography for measuring plasma hydromorphone concentrations in human subjects.

## Methods

### *Subjects*

Ten healthy volunteers, men between 21 and 38 yr of age with body weights of 63.4–99.2 kg (mean, 72.7 kg) were recruited for this study. All subjects were within ±10% of norms for body weight and height. All subjects gave informed consent as approved by the Institutional Review Board of Fred Hutchinson Cancer Research Center.

### *Subject Preparation*

On each test day, we placed 22-gauge catheters in the basilic vein of the subject's left arm for drug administration and in the right arm for blood sampling. We drew blood samples into heparinized syringes just before and 1, 2, 3, 4, 5, 7, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, and 300 min after a 45-s injection of 10, 20, or 40 μg/kg of hydromorphone (calculated as base). Blood samples were placed on ice until the end of each test session and then were centrifuged to obtain plasma samples. Plasma was stored at −40°C for later assay of hydromorphone concentration. A minimum of 7 days separated all hydromorphone doses in each subject. We randomized the order of administration of the three doses within and across subjects.

### *Hydromorphone Assay*

We employed a modification of the general method of Todd et al. (11). For extraction of hydromorphone, 1-mL aliquots of plasma were thoroughly mixed with 1.5 mL sodium borate buffer (pH 8.96) and the internal standard (20 ng nalorphine). Samples were applied to liquid-liquid extraction columns (Chem-Elute CE1003) and allowed to equilibrate for 5 min. We eluted hydromorphone and nalorphine from the columns with two 5-mL portions of chloroform/isopropanol (95:5). We evaporated the organic solvent completely with a stream of nitrogen at 45°C, redissolved the residue in 400 μL mobile phase, and injected 20 μL for chromatographic analysis. Extraction recoveries for hydromorphone from plasma averaged 87% with a 9.1% coefficient of variation.

We performed hydromorphone analyses on a Varian 5060 high-performance liquid chromatograph using an ESA coulometric detector set at +0.75, 0.25, and 0.45 V for guard, cell 1, and cell 2, respectively. A Supelco C18DB column (15 cm × 4.6 mm, 5-μm particle size) and a guard column of the same material were used. The column was heated to 40°C. The mobile phase was 0.07 M phosphate buffer at pH 3.47, methanol, acetonitrile (87:9:4) at a flow rate of 1.0 mL/min. Within-day coefficients of variation at 1, 5, 10, and 20 ng/mL were 6.8%, 6.3%, 4.5%, and 4.0%, respectively, as determined with samples of blank human plasma to which known amounts of hydromorphone and internal standard were added ($n$ = 10–12 samples per concentration). Between-day coefficient of variation at 20 ng/mL was 6.7%. The detection limit for hydromorphone was 0.1 ng/mL (3 × signal/noise).

### *Data Analysis*

Plasma hydromorphone concentration versus time data from each subject at each dose were fit to biexponential and triexponential decay curves by nonlinear least-squares regression with constant weighting of 1/variance, with variance estimated as the predicted concentration squared (12). We chose the best fit in each case based on the lesser sum of

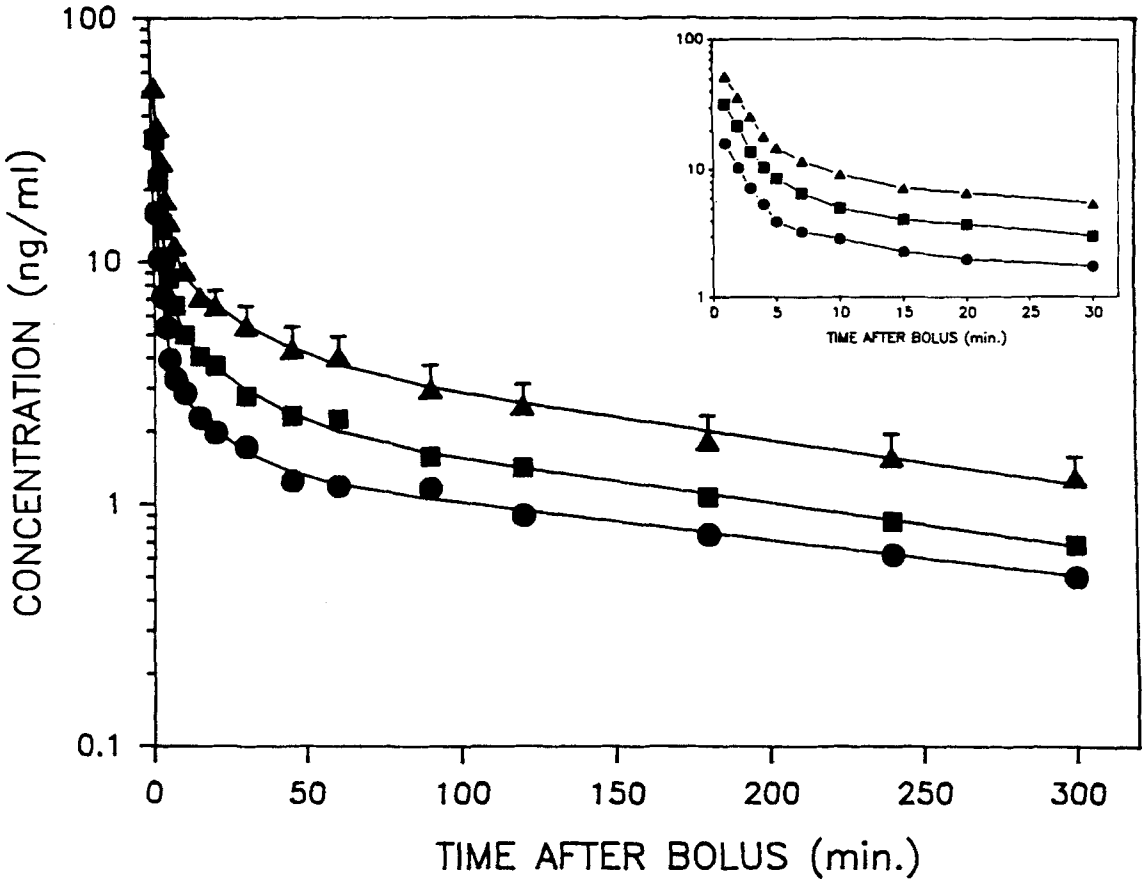


Figure 1. Plasma concentrations of hydromorphone after intravenous bolus doses. Values are mean (±SE) for 10 subjects at each dose. Data points are measured concentrations, and lines represent the nonlinear least-squares fits of the mean concentration-versus-time data at each dose. ●, 10 μg/kg; ■, 20 μg/kg; ▲, 40 μg/kg.

squared residuals with adjustment for the number of exponentials according to Akaike (13). We used individual subject exponential coefficients for $Cp = Pe^{-\pi t} + Ae^{-\alpha t} + Be^{-\beta t}$ to calculate distributional half-lives, central compartment volume, and hybrid rate constants; total clearance and steady-state distribution volume were calculated from area under the concentration-time curve (AUC, extrapolated to infinity using the last measured concentration/$\beta$) and AUMC, the first moment of AUC (14). Differences across doses in the mean pharmacokinetic parameters were examined by analysis of variance for significance ($P < 0.05$).

## Results

The mean measured concentrations ($n = 10$) of hydromorphone at each sampling time are shown in Figure 1. Nonlinear least-squares fits of the mean data for each dose indicated that the hybrid rate constants for net loss of hydromorphone from plasma were very similar across doses for the group of subjects.

All individual concentration-versus-time data sets were best described by triexponential (versus biexponential) equations for each subject and dose according to standard criteria (13). Individual subject values for the constants and exponents of the triexponential decay curves are shown in Table 1. There was a two- to eightfold variation across subjects in values for each coefficient.

The triexponential coefficients, along with AUC and mean residence time (MRT), are shown as group means and standard error in Table 2. The exponential coefficients (P, A, B) as well as AUC were linearly related to dose, as expected. There were no significant differences in the rate constants ($\pi$, $\alpha$, $\beta$) or MRT across doses.

Standard pharmacokinetic parameters are displayed in Table 3. Again, we found no significant dose-related differences for any of the parameters. For each pharmacokinetic parameter, individual sub-

Table 1. Triexponential Coefficient Rate Constants for Individual Subjects

| | 10 μg/kg | | | | | | 20 μg/kg | | | | | | 40 μg/kg | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dose | P | A | B | π | α | β | P | A | B | π | α | β | P | A | B | π | α | β |
| 1 | 52.6 | 3.0 | 1.2 | 0.64 | 0.060 | 0.0046 | 51.1 | 7.7 | 2.6 | 0.70 | 0.068 | 0.0038 | 181 | 22.1 | 3.4 | 1.5 | 0.116 | 0.0057 |
| 2 | 8.1 | 2.3 | 1.2 | 0.39 | 0.026 | 0.0019 | 52.1 | 5.8 | 2.8 | 1.2 | 0.109 | 0.0049 | 123 | 12.2 | 6.8 | 1.1 | 0.136 | 0.0056 |
| 3 | 31.4 | 1.8 | 0.9 | 0.55 | 0.017 | 0.0023 | 56.9 | 3.2 | 2.6 | 0.55 | 0.033 | 0.0030 | 54.7 | 3.5 | 5.6 | 0.48 | 0.034 | 0.0050 |
| 4 | 10.9 | 3.7 | 1.2 | 0.35 | 0.082 | 0.0071 | 34.8 | 6.2 | 2.3 | 0.66 | 0.078 | 0.0051 | 48.8 | 6.7 | 2.8 | 0.46 | 0.021 | 0.0027 |
| 5 | 20.6 | 2.7 | 1.5 | 0.70 | 0.090 | 0.0038 | 35.9 | 6.1 | 1.6 | 0.57 | 0.064 | 0.0035 | 50.9 | 3.5 | 4.4 | 0.34 | 0.024 | 0.0021 |
| 6 | 14.7 | 1.7 | 1.0 | 0.43 | 0.054 | 0.0028 | 52.1 | 2.6 | 1.5 | 0.43 | 0.050 | 0.0028 | 82.1 | 12.3 | 4.3 | 0.59 | 0.143 | 0.0050 |
| 7 | 16.4 | 0.8 | 1.2 | 0.47 | 0.055 | 0.0121 | 41.2 | 6.2 | 2.9 | 1.1 | 0.114 | 0.0095 | 45.9 | 4.6 | 4.0 | 0.47 | 0.067 | 0.0069 |
| 8 | 10.6 | 0.8 | 0.9 | 0.29 | 0.025 | 0.0018 | 45.8 | 3.4 | 1.8 | 0.43 | 0.023 | 0.0023 | 54.6 | 7.3 | 5.0 | 0.40 | 0.039 | 0.0055 |
| 9 | 46.2 | 1.5 | 1.8 | 0.93 | 0.045 | 0.0039 | 34.1 | 3.6 | 2.4 | 0.47 | 0.054 | 0.0046 | 119 | 10.3 | 4.5 | 0.71 | 0.062 | 0.0064 |
| 10 | 30.5 | 2.5 | 1.6 | 0.77 | 0.072 | 0.0051 | 101 | 6.8 | 3.0 | 0.79 | 0.061 | 0.0042 | 137 | 12.9 | 4.7 | 0.69 | 0.068 | 0.0040 |
| CV% | 61 | 43 | 23 | 35 | 45 | 55 | 37 | 33 | 22 | 37 | 42 | 44 | 50 | 57 | 23 | 50 | 61 | 30 |
| Range[a] | 6.5 | 4.0 | 2.0 | 3.2 | 5.3 | 6.3 | 3.0 | 2.9 | 1.8 | 2.7 | 4.8 | 4.1 | 3.7 | 6.2 | 2.4 | 4.3 | 6.8 | 3.3 |

P, A, and B are exponential coefficients in ng/mL and $\pi$, $\alpha$, and $\beta$ are hybrid rate constants in $min^{-1}$. Coefficients of variation (CV% = SD/mean × 100) provide an index for comparison of relative variation in individual values across coefficients and doses.

[a]Range = highest value/lowest value.

Table 2. Analysis of Variance: Coefficients and AUC for Triexponential Fits of Individual Subject Data

| | 10 μg/kg | 20 μg/kg | 40 μg/kg | F | P |
|---|---|---|---|---|---|
| P | 24.21 (4.90) | 50.49 (6.19) | 89.68 (14.97) | 15.40 | 0.000 |
| A | 2.08 (0.30) | 5.17 (0.56) | 9.53 (1.81) | 9.77 | 0.001 |
| B | 1.26 (0.10) | 2.35 (0.17) | 4.54 (0.35) | 51.41 | 0.000 |
| $\pi$ | 0.552 (0.064) | 0.686 (0.083) | 0.671 (0.112) | 0.26 | 0.717 |
| $\alpha$ | 0.053 (0.009) | 0.065 (0.010) | 0.070 (0.014) | 0.15 | 0.862 |
| $\beta$ | 0.0045 (0.0010) | 0.0044 (0.0006) | 0.0049 (0.0005) | 0.17 | 0.845 |
| AUC | 500 (72) | 757 (68) | 1319 (145) | 40.80 | 0.000 |
| MRT | 240 (54) | 207 (23) | 185 (30) | 1.40 | 0.220 |

AUC is the area under the plasma concentration versus time curve ($ng \cdot mL^{-1} \cdot min^{-1}$), and MRT is mean residence time (min). P, A, and B (ng/mL) and $\pi$, $\alpha$, and $\beta$ ($min^{-1}$) are defined in the text.

Values are group means with standard errors in parentheses.

ject values varied over a two- to sixfold range, reflecting large intersubject variation in the triexponential coefficients.

At each dose, the "intercompartmental" transfer rate constant $k_{31}$ was much lower than $k_{21}$ and $k_{10}$ (elimination rate constant). In the context of a three-compartment mammillary model (Figure 2), this indicates that movement of hydromorphone from a set of tissues ($V_B$) that slowly equilibrates with blood governs the rate of terminal elimination of the opioid after an intravenous bolus dose.

In Table 4, we present a comparison of plasma hydromorphone concentrations (for the 40-μg/kg dose) measured by high-performance liquid chromatography in this study and as measured by two different radioimmunoassay methods in previously reported studies using 2-mg intravenous doses (corresponding to 23.2 μg base/kg in Vallner et al. [6] and 25.8 μg base/kg in Parab et al. [7]) for selected times after the bolus doses. In each of the previous studies using radioimmunoassays, measured hydromorphone concentrations were higher than those produced by an even larger dose of the opioid when concentrations are measured by high-performance liquid chromatography (this study).

## Discussion

In all subjects at all doses, we found three distinct phases of hydromorphone loss from plasma after intravenous bolus injections. The first phase ($\pi$) has not been characterized previously. In contrast to previous studies, we were able to define this "fast distributional" phase by sampling blood frequently at early times after hydromorphone injections. Distributional properties of hydromorphone are very similar

Table 3. Pharmacokinetic Parameters for Three Doses of Hydromorphone

| | 10 μg/kg | 20 μg/kg | 40 μg/kg | P | Pooled mean |
|---|---|---|---|---|---|
| $t_{1/2\pi}$ (min) | 1.40 (0.17) | 1.13 (0.12) | 1.25 (0.16) | 0.624 | 1.27 (0.08) |
| $t_{1/2\alpha}$ (min) | 16.2 (2.7) | 13.2 (2.3) | 14.8 (3.2) | 0.724 | 14.7 (1.5) |
| $t_{1/2\beta}$ (min) | 208.0 (34.0) | 182.6 (20.6) | 162.0 (23.6) | 0.171 | 184.2 (15.0) |
| Cl (L/min) | 1.51 (0.30) | 1.61 (0.19) | 1.85 (0.20) | 0.303 | 1.66 (0.13) |
| $V_c$ (L) | 26.2 (4.2) | 22.8 (2.2) | 26.2 (3.7) | 0.476 | 24.4 (2.0) |
| $Vd_{ss}$ (L) | 283 (24) | 300 (20) | 301 (24) | 0.702 | 295 (13) |
| $k_{12}$ | 0.260 (0.039) | 0.322 (0.043) | 0.307 (0.052) | 0.804 | 0.296 (0.025) |
| $k_{21}$ | 0.110 (0.018) | 0.143 (0.023) | 0.142 (0.023) | 0.850 | 0.131 (0.011) |
| $k_{13}$ | 0.153 (0.026) | 0.194 (0.025) | 0.190 (0.043) | 0.706 | 0.179 (0.018) |
| $k_{31}$ | 0.017 (0.002) | 0.017 (0.003) | 0.019 (0.002) | 0.888 | 0.018 (0.001) |
| $k_{10}$ | 0.071 (0.013) | 0.079 (0.008) | 0.089 (0.019) | 0.874 | 0.0080 (0.008) |

$t_{1/2\pi}$ and $t_{1/2\alpha}$ are distributional half-lives and $t_{1/2\beta}$ is the elimination half-life; $Cl_s$ = systemic clearance. $V_c$ and $Vd_{ss}$ are central compartment and steady-state distribution volumes, respectively. $k_{12}$, $k_{21}$, $k_{13}$, and $k_{31}$ are first-order intercompartmental transfer rate constants ($min^{-1}$) between the central and shallow or deep compartments. $k_{10}$ = elimination rate constant (central compartment).

Means and standard errors of individual subject values for each dose level are presented along with mean values for all subjects at all doses.

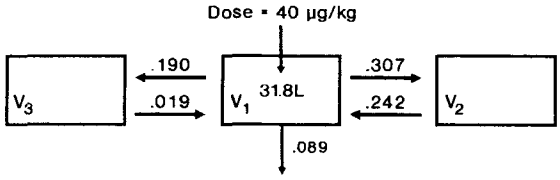


Figure 2. Compartmental model for hydromorphone distribution and elimination (40 μg/kg IV). $V_1$ represents the central compartment (Vc in text).

Table 4. Comparison of Hydromorphone Plasma Concentrations (ng/mL) at Selected Times After Intravenous Bolus Doses

| Time (min) | Vallner et al. (6) (23.2 μg/kg) | Parab et al. (7) (25.8 μg/kg) | Hill et al.[a] (40 μg/kg) |
|---|---|---|---|
| 15 | 28 | 20 | 7 |
| 30 | 20 | 9 | 5 |
| 60 | 18 | 5 | 4 |
| 120 | 13 | 3 | 2.5 |

[a]The present study.

to those reported for morphine (15–17). We found that about 90% of hydromorphone is lost from plasma within 10 min after a 45-s injection. This rapid loss of hydromorphone from blood presumably to highly perfused tissues occurs with a mean hybrid rate constant of 0.636/min, about 10 times more rapidly than redistribution to other tissues ($\alpha$ = 0.063/min). It should be noted that because we used forearm venous sampling here, initial local drug distribution may have accounted for some systemic drug loss during the early sampling period. Also, we used a brief infusion (45 s) instead of a true bolus delivery for the hydromorphone injections and that may also limit the accuracy of the estimations of initial hydromorphone distribution characteristics. Nonetheless, this apparent initial phase of rapid redistribution of hydromorphone is similar to that of morphine after intravenous bolus doses with peripheral venous sampling in normal volunteers (18) and in cancer patients with central venous sampling (19).

Comparison of the intercompartmental transfer rate constants and elimination rate constants indicates that the rate of diffusion of hydromorphone from one of the tissue "compartments" to plasma governs the terminal elimination of hydromorphone from the body ($k_{31} << k_{21}$, $k_{10}$). This dependence of hydromorphone elimination on extensive tissue uptake and slow release of hydromorphone from tissue to blood is very similar to the kinetic behavior of morphine (15), fentanyl (20), and methadone (21), in contrast to alfentanil, which distributes less extensively from plasma to tissues than do other μ-receptor agonists (22).

Our findings with hydromorphone present a further example of the substantial pharmacokinetic variability across subjects that is characteristic of opioids. The triexponential coefficients varied over a two- to eightfold range in this group of subjects. This is very similar to the large intersubject pharmacokinetic variability reported for meperidine (23), morphine (16), fentanyl (24), alfentanil (20), and nalbuphine (17). This pharmacokinetic variability probably contributes importantly to the variable clinical response to a fixed dose of hydromorphone. The results of this study reinforce the desirability of administering hydromorphone on the basis of individual patient need for pain relief instead of using a standard dose for pain control. As with other opioids, use of hydromorphone via patient-controlled analgesia techniques

should obviate or diminish the impact of pharmacokinetic variability on adequate dosing.

In the two previous studies of hydromorphone pharmacokinetics, radioimmunoassays using morphine antibodies were employed to measure plasma hydromorphone concentrations. Catlin (25) demonstrated substantial variation in cross-reactivity of different batches of radioimmunoassay antibody with morphine and its glucuronide metabolites. Unlike radioimmunoassay, the high-performance liquid chromatography method used in this study does not detect morphine glucuronides (or normorphine) as morphine. The higher plasma concentrations found at each time point by radioimmunoassay may be due to antibody cross-reactivity with hydromorphone metabolites (e.g., hydromorphone-3-glucuronide). The glucuronide metabolites of morphine have longer elimination half-lives and lower clearances and volumes of distribution than morphine (26,27). If the same is true of hydromorphone glucuronides, then the pharmacokinetic parameters reported earlier for this opioid would be expected to differ from those reported here.

Pharmacokinetic linearity with dose is a very desirable feature relevant to clinical use of opioids and should be examined routinely in pharmacokinetic studies (28). Hydromorphone pharmacokinetics are not dose-dependent over the fourfold range of doses studied here. This is similar to results reported for morphine (15) and other opioids (20,21). Our estimation of terminal elimination rate constants and terminal half-life could be inaccurate because the last blood samples were obtained only 5 h after the hydromorphone doses. However, the excellent fits of each subject's data and the grouped data at each dose (see Figure 1) by the triexponential model employed here during the 90–300-min period indicate that this does represent the terminal elimination phase for hydromorphone. Half-lives determined by separately fitting monoexponential equations to the 90–300-min data sets of the individual subjects were very similar to the terminal elimination half-lives ($t_{1/2\beta}$ values) derived from the triexponential equations, indicating further that either the latter are valid estimates or a terminal hydromorphone elimination phase exists that does not begin to be evident until more than 5 h after dosing.

We are beginning to understand the relationship between plasma opioid concentration, analgesic effects, and side-effect liabilities for opioid analgesics that are selective $\mu$-receptor agonists (18,29,30). For hydromorphone, Reidenberg et al. (8) reported that the minimally effective plasma concentration in patients with chronic severe pain is about 4 ng/mL. In studies using continuous hydromorphone infusions in patients with cancer pain, Inturrisi et al. (31) found that half-maximal pain relief was produced by a plasma hydromorphone concentration of about 20 ng/mL ($Css_{50}$), whereas the $Css_{50}$ for sedation was about twice that value. However, in both of these studies there was considerable intersubject variability in the pharmacokinetic-pharmacodynamic relationships. Steady-state studies are needed to clarify the relationship between plasma hydromorphone concentration and magnitudes of pharmacologic effects (18,30); these have not yet been done.

We thank Dr. Gary Donaldson for performing statistical analyses for this study and Kathy Andrus for expert assistance with the hydromorphone assays.

## References

1. Mahler DL, Forrest WH Jr. Relative analgesic potencies of morphine and hydromorphone in postoperative pain. Anesthesiology 1975;42:602–7.
2. Hanna C, Mazuzan JE Jr, Abajian J Jr. An evaluation of dihydromorphinone in treating postoperative pain. Anesth Analg 1962;41:755–61.
3. Roy SD, Flynn GL. Solubility and related physicochemical properties of narcotic analgesics. Pharm Res 1988;5:580–6.
4. Parab PV, Coyle DE, Streng WH, Denson DD, Ritschel WA. Biopharmaceutic parameters of hydromorphone and in-vitro evaluation of its tablet and suppository dosage form. Pharm Ind 1987;49:951–6.
5. Cone EJ, Phelps BA, Gorodetzky CW. Urinary excretion of hydromorphone and metabolites in humans, rats, dogs, guinea pigs, and rabbits. J Pharm Sci 1977;66:1709–13.
6. Vallner JJ, Stewart JT, Kotzan JA, Kirsten EB, Honigberg IL. Pharmacokinetics and bioavailability of hydromorphone following intravenous and oral administration to human subjects. J Clin Pharmacol 1981;21:152–6.
7. Parab PV, Ritschel WA, Coyle DE, Gregg RV, Denson DD. Pharmacokinetics of hydromorphone after intravenous, peroral and rectal administration to human subjects. Biopharm Drug Dispos 1988;9:187–99.
8. Reidenberg MM, Goodman H, Erle H, et al. Hydromorphone levels and pain control in patients with severe chronic pain. Clin Pharmacol Ther 1988;44:376–82.
9. Kerr IG, Sone M, DeAngelis C, Iscoe N, MacKenzie R, Schueller T. Continuous narcotic infusion with patient-controlled analgesia for chronic cancer pain in outpatients. Ann Intern Med 1988;108:554–7.
10. Coda B, Tanaka A, Hill H, Iverson K. Dose effects of hydromorphone in human analgesia. Pain 1990;(Suppl 5):S189.
11. Todd RD, Muldoon SM, Watson RL. Determination of morphine in cerebrospinal fluid and plasma by high performance liquid chromatography with electrochemical detection. J Chromatogr Biomed Appl 1982;232:101–10.
12. Knott GD. Mlab—a mathematical modeling tool. Comput Programs Biomed 1979;10:271–80.
13. Akaike H. Fitting autoregressive models for prediction. Ann Inst Stat Math 1969;21:243–7.

14. Gibaldi M, Perrier D, eds. Pharmacokinetics. 2nd ed. New York: Marcel Dekker, 1982.
15. Murphy MR, Hug CC Jr. Pharmacokinetics of intravenous morphine in patients anesthetized with enflurane-nitrous oxide. Anesthesiology 1981;54:187–92.
16. Stanski DR, Greenblatt DJ, Lappas DG, Koch-Wester J, Lowenstein E. Kinetics of high-dose intravenous morphine in cardiac surgery patients. Clin Pharmacol Ther 1976;19:752–6.
17. Aitkenhead AR, Vater M, Achola K, Cooper CMS, Smith G. Pharmacokinetics of single-dose I.V. morphine in normal volunteers and patients with end-stage renal failure. Br J Anaesth 1984;56:813–9.
18. Hill HF, Saeger L, Bjurstrom R, Donaldson G, Chapman CR, Jacobson R. Steady-state infusions of opioids in human volunteers. I. Pharmacokinetic tailoring. Pain 1990;43:57–67.
19. Hill HF, Jacobson RC, Coda BA, Mackie AM. A computer-based system for controlling plasma opioid concentrations according to patient need for analgesia. Clin Pharmacokinet (in press).
20. Bower S, Hull CJ. Comparative pharmacokinetics of fentanyl and alfentanil. Br J Anaesth 1982;54:871–8.
21. Nilsson MI, Meresaar U, Angaard E. Clinical pharmacokinetics of methadone. Acta Anaesthesiol Scand 1982;74:66–9.
22. Mather LE. Clinical pharmacokinetics of fentanyl and its newer derivatives. Clin Pharmacokinet 1983;8:422–46.
23. Austin KL, Stapleton JV, Mather LE. Relationship between blood meperidine and analgesic response: a preliminary report. Anesthesiology 1986;53:460–6.
24. Reilly CS, Wood AJ, Wood M. Variability of fentanyl pharmacokinetics in man. Anaesthesia 1984;40:837–43.
25. Catlin DH. Pharmacokinetics of morphine by radioimmunoassay: the influence of immunochemical factors. J Pharmacol Exp Ther 1977;200:224–35.
26. Sawe J, Kager L, Svensson Eng J-O, Rane A. Oral morphine in cancer patients: in vivo kinetics and in vitro hepatic glucuronidation. Br J Clin Pharmacol 1985;19:495–501.
27. Osborne R, Joel S, Trew D, Slevin M. Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. Clin Pharmacol Ther 1990;47:12–9.
28. Van Rossum JM, van Lingen G. Dose-dependent pharmacokinetics. In: Rowland M, Tucker G, eds. International encyclopedia of pharmacology and therapeutics, section 122.
29. Gourlay GK, Kowalski SR, Plummer JL, Cousins MJ, Armstrong PJ. Fentanyl blood concentration-analgesic response relationship in the treatment of postoperative pain. Anesth Analg 1988;67:329–37.
30. Hill HF, Chapman CR, Saeger L, et al. Steady-state infusions of opioids in human. II. Concentration-effect relationships and therapeutic margins. Pain (in press).
31. Inturrisi C, Portenoy R, Stillman M, Colburn W, Foley K. Hydromorphone bioavailability and pharmacokinetic-pharmacodynamic (PK-PD) relationships. Am Soc Clin Pharmacol Ther 1988;43:162.