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Influence of Age on the Pharmacokinetics and Pharmacodynamics of Oral Transmucosal Fentanyl Citrate

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Background: **Cancer pain is primarily a problem of older persons. Oral transmucosal fentanyl citrate (OTF) was developed to provide rapid analgesia and is the first drug specifically approved for treating breakthrough cancer pain. Fentanyl in OTF is absorbed across the oral mucosa but a considerable portion is swallowed and absorbed enterally. The effects of age on OTF pharmacokinetics and pharmacodynamics are unknown. This investigation evaluated OTF disposition and clinical effects in older (60–75 yr) compared with younger (18–40 yr) volunteers.**

Methods: **Healthy young (26 ± 6 yr) and older (67 ± 6 yr) volunteers (n = 12 each) were studied in an Institutional Review Board approved protocol. They received OTF (10 μg/kg). Plasma fentanyl and norfentanyl concentrations were determined by mass spectrometry. Fentanyl effects were measured by dark-adapted pupil diameter and by subjective self-assessments using visual analog scales.**

Results: **Plasma fentanyl and norfentanyl concentrations and pharmacokinetic parameters did not differ between younger and older subjects. Maximum pupil diameter change from baseline was significantly less in older (3.1 ± 0.7 mm) compared with younger (4.5 ± 1.1 mm) subjects ($P < 0.05$). OTF-dependent subjective assessments of alertness/sedation, energy level, confusion, clumsiness, anxiety, and nausea did not differ in the older subjects.**

Discussion: **The pharmacokinetics of OTF were not altered in older volunteers. In contrast, there was a somewhat diminished response to the miotic effects of fentanyl in older subjects. No change in OTF dosing in the elderly would appear necessary because of altered pharmacokinetics. If the response to OTF in older patients is similar to that in older volunteers and miosis is representative of analgesia and respiratory depression, then changes in OTF dosing with age alone do not appear indicated.**

PAIN is primarily a problem of older persons, both for cancer pain and nonmalignant pain.[1] The incidence of cancer in the Western world increases with age, and approximately half of all cancers occur in patients older than 65 yr.[2] Approximately one third of cancer patients have pain at diagnosis and 70–90% suffer pain with advanced disease.[3–5] Treatment of cancer pain in older patients is also more challenging because of the increased risk of therapeutic complications resulting from the loss of physiologic reserve, comorbidities, geriatric syndromes, and decline in cognitive function.[2] Cognitive impairment occurs both in aging and in advanced cancer.[6] Benign noncancer pain also increases with age, with a prevalence among older (>65) patients as high as 70–80%.[1]

Opioids are a mainstay in cancer pain management. More than half of all cancer patients have severe pain requiring World Health Organization step 3 strong opioids (morphine, methadone fentanyl, buprenorphine).[7] In addition to scheduled opioids, 40–80% of cancer patients require rapid-onset, short-acting opioids for breakthrough pain, defined as "a transitory exacerbation of pain to severe or excruciating levels that occurs on a background of otherwise stable mild or moderate pain in a patient receiving chronic opioid therapy."[7–10] Oral transmucosal fentanyl citrate (OTF)[11] was the first drug specifically approved for treating breakthrough cancer pain.[12] OTF is effective (>90% response), has a rapid onset (mean 10 min) and short duration, and allows increased patient activity with improved well-being.[12,13] OTF provides faster analgesia, better pain relief, and greater patient satisfaction than conventional rescue opioids.[13–17]

OTF pharmacokinetics represent a composite of transmucosal and enteral absorption. Specifically, after OTF placement between the cheek and lower gum and rubbing against the mucosal surface, approximately 25% undergoes oral transmucosal absorption and a significant portion (75%) is swallowed, absorbed intestinally, and subject to first-pass metabolism (two thirds of the swallowed dose), with an overall bioavailability of 50% (equally from transmucosal absorption and swallowed fentanyl escaping first-pass metabolism).[18] Although several investigations have carefully evaluated OTF pharmacokinetics, all were conducted in young, healthy volunteers.[18–21] As outlined above, this is nonrepresentative of the majority of the population actually using OTF. The pharmacokinetics and pharmacodynamics of OTF in older subjects is unknown. Furthermore, the disposition of fentanyl in older individuals, in general, is not well characterized. Therefore the purpose of this investigation was to evaluate the effect of age on the disposition and clinical effects of OTF.

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Materials and Methods

Clinical Protocol

The investigation was approved by the University of Washington Institutional Review Board and carried out

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in accordance with the Declaration of Helsinki, and each subject provided written informed consent. Twelve healthy subjects (six men, six women, aged 67 ± 4 yr, weighing 72 ± 14 kg) were studied. Eligibility criteria were age 60–75 yr within 30% of ideal body weight. The comparison group was 12 healthy younger (eligibility, 18–40 yr) subjects (six men, six women, aged 26 ± 6 yr, weighing 69 ± 15 kg) studied contemporaneously as part of a four-way drug-interaction protocol using data from the control arm of the study. Details of that protocol are in the accompanying publication.[22] Exclusion criteria for all subjects included a history of liver or renal disease, pregnancy or nursing, taking drugs or herbals known to induce or inhibit CYP3A enzymes (including oral contraceptives), a history of addiction to alcohol or drugs (previous or current addiction or treatment for addiction), and access to and routine handling of addicting drugs in the regular course of subjects' professional duties. Subjects were instructed to abstain from grapefruit products for at least 5 days before and during the study session, from alcohol and caffeine for at least 24 h before and during the study session, and to fast for a minimum of 8 h before opioid administration. Each subject was studied once.

For each study session, a peripheral intravenous catheter was inserted for drug administration and blood sampling. All subjects (recumbent) were monitored *via* electrocardiogram, blood pressure, and pulse oximeter. If the subject's oxyhemoglobin saturation decreased to less than 94%, they were prompted to breathe deeply. Supplemental oxygen (2–3 l/min nasal prongs) was given if saturation did not increase to 94% or if the subject was prompted more than three times within any 5-min period. All subjects received ondansetron (4 mg, intravenous). Thirty min later, they received OTF (target dose 10 μg/kg, as either a 600 or 800 μg lozenge). The OTF dose was 600 and 800 μg, respectively, in four and eight older subjects and eight and four younger subjects. Subjects were advised to rub the medication across the buccal mucosa and to not bite, suck, or chew the lozenge. Subjects were monitored to pace dissolution of the medication over exactly 15 min. The start of OTF administration was time zero. Venous blood samples were obtained at baseline, every 5 min during dosing, and 5, 10, 15, 20, 30, 45, 60, 90, 120, 240, 360, 480, and 600 min after completion of OTF administration. Plasma was separated and stored at −20°C for later analysis. Dark-adapted pupil diameters were determined coincident with blood sampling, as described previously,[23] except that a Pupilscan Model 12A pupillometer (Keeler Instruments Inc., Broomall, PA) was used. Nausea or vomiting were treated with ondansetron (4 mg intravenous or 8 mg orally) as needed.

Subjective self-assessment of fentanyl effect was quantified by visual analog scales (scored from 0 to 100) for levels of alertness/sedation (almost asleep to wide awake), energy level (no energy to full of energy), confusion (confused to clear headed), clumsiness (extremely clumsy to well coordinated), anxiety (calm/relaxed to extremely nervous), and nausea (no nausea to worst nausea). Fentanyl and norfentanyl were quantified by high pressure liquid chromatography-electrospray mass spectrometry as described previously.[22]

Plasma fentanyl and norfentanyl data were analyzed using a noncompartmental model with extravascular input (WinNonlin 4.01, Pharsight Corp, Mountain View, CA). Pupil diameter data were also analyzed using noncompartmental methods, as described previously.[23] Concentration-effect data were analyzed by nonparametrically collapsing the hysteresis loops to determine the value of k_{e0}, the first order rate constant for transfer between plasma, and the effect compartment[24] using the program ke0obj.§

Unpaired Student *t* tests or the Mann-Whitney rank sum test were used to assess the significance of differences between groups for pharmacodynamic and effect parameters, using SigmaStat (SPSS Science, Chicago, IL). Visual analog scores were analyzed by two-way repeated measures analysis of variance followed by the Student-Newman-Keuls test. All results are reported as the mean ± SD. Statistical significance was assigned at $P < 0.05$.

Results

Plasma concentrations of fentanyl and norfentanyl after OTF are shown in figure 1. Secondary peaks in fentanyl concentrations were apparent in half of the subjects. Plasma fentanyl concentrations at the early time points were numerically higher in the elderly subjects; however, this difference was neither statistically nor clinically significant. There was no significant difference between young and elderly subjects at any time point for both fentanyl and norfentanyl concentrations. Aside from a minor difference in the time of the second plasma fentanyl peak, there were no significant differences between young and elderly subjects in any pharmacokinetic parameter for fentanyl or norfentanyl (table 1). Results in table 1 are not adjusted for dose. There were also no differences between groups in dose-adjusted values (not shown).

OTF effects were characterized using dark-adapted pupil diameter (fig. 2), and miosis *versus* time data were analyzed similarly to fentanyl concentration *versus* time data to obtain effect parameters (table 2). Baseline dark-adapted pupil diameters were significantly smaller in the elderly subjects (5.5 ± 0.9 *versus* 8.6 ± 0.9 mm). Nevertheless, in both groups, the time course of pupil diameters after OTF administration (fig. 2) strongly resembled the time course of plasma fentanyl concentration (fig. 1).

§ Available at http://anesthesia.stanford.edu/pkpd/. Accessed August 23, 2003.

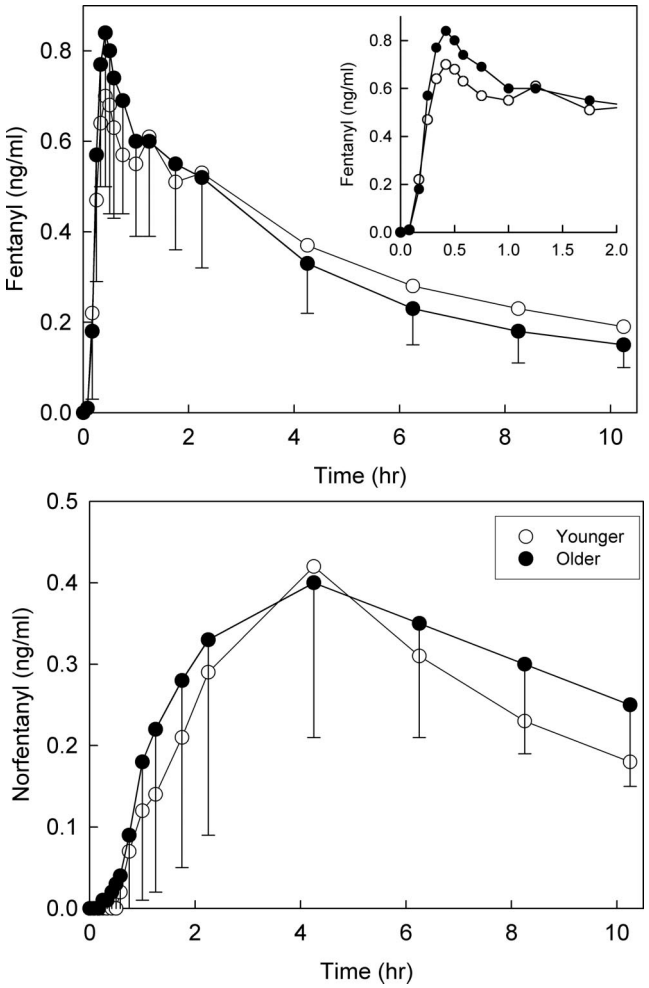

Fig. 1. Effect of age on plasma fentanyl and norfentanyl concentrations after oral transmucosal fentanyl citrate. The inset magnifies the results at early time points. Results are mean ± SD (n = 12). Some SD are omitted for clarity.

After correcting for baseline differences in pupil diameter by calculating the pupil diameter change from predose diameter (*i.e.*, miosis), there was a significant difference between young and elderly subjects in the degree of miosis (fig. 2). Time-specific miosis was significantly less in the elderly subjects from 0.4–4.2 h after OTF administration. Maximum miosis and time to maximum miosis were significantly different in elderly subjects. There was considerable interindividual variability in miosis area under the curve *versus* time, and differences between elderly and young subjects were not significant.

Subjective effects of OTF were somewhat less in elderly subjects (fig. 3). Visual analog scores for sedation, confusion, and clumsiness demonstrated less drug effect at multiple time points in the elderly patients. This observation is tempered, however, by appreciable baseline differences (lower scores in young subjects); this was statistically significant for clumsiness.

Fentanyl concentration-effect relationships after OTF were evaluated using miosis and presented as a hysteresis plot (fig. 4). There was counterclockwise hysteresis, consistent with the small delay in onset after fentanyl. In elderly subjects, the hysteresis loop was shifted downward, indicating diminished response. Nonetheless, there was no change in the overall shape of the hysteresis loops and specifically no divergence of the ascending and descending limbs that would have reflected diminished entry of fentanyl to the site of action. The fentanyl k_{e0} for miosis (table 2) was not significantly different with age.

The experimental protocol was safely conducted without serious adverse events. Respiratory depression, defined as an oxygen saturation <94% and need for supplemental oxygen, occurred in one young control subject and in nine elderly subjects. The greater incidence of low oxygen saturation in the elderly subjects is consistent with the known age-related decline in pulmonary oxygenation and the lower starting oxygen saturation in this group (97 ± 2 *versus* 99 ± 1%), and it required no further intervention. Treatment of nausea or vomiting was required in one young and two elderly subjects.

Discussion

This investigation is the first to characterize the pharmacokinetics and clinical effects of OTF in the elderly. The primary purpose was to assess the effect of age on

Table 1. Oral Transmucosal Fentanyl Pharmacokinetic Parameters

	Younger Subjects	Older Subjects
Fentanyl		
Cmax1† (ng/ml)	0.74 ± 0.34	0.90 ± 0.32
Cmax2 (ng/ml)	0.75 ± 0.67 (7)	0.69 ± 0.22 (6)
Tmax1 (h)	0.42 ± 0.08	0.46 ± 0.09
Tmax2 (h)	1.9 ± 0.5 (7)	1.3 ± 0.5* (6)
AUC_{0-10} (h · ng/ml)	3.62 ± 1.96	3.42 ± 1.03
$AUC_{0-\infty}$ (h · ng/ml)	5.87 ± 3.74	4.40 ± 1.30
Kel (1/h)	0.127 ± 0.046	0.162 ± 0.045
CL/F (l/h)	153 ± 78	179 ± 58
V/F (l)	1240 ± 400	1150 ± 370
Bioavailability‡	0.50 ± 0.25	0.36 ± 0.10
Norfentanyl		
Cmax (ng/ml)	0.49 ± 0.26	0.44 ± 0.21
Tmax (h)	4.0 ± 2.0	4.4 ± 2.4
AUC_{0-10} (h · ng/ml)	2.60 ± 0.72	3.04 ± 1.38
$AUC_{0-\infty}$ (h · ng/ml)	4.70 ± 2.20	6.91 ± 2.76*
$AUC_{0-10\ norfentanyl/fentanyl}$	0.92 ± 0.63	0.94 ± 0.47

AUC_{0-10} = area under the curve of plasma concentration *versus* time from 0–10 h; $AUC_{0-\infty}$ = area under the curve of plasma concentration *versus* time from time zero extrapolated to infinity; CL/F = apparent oral clearance; Cmax = maximum plasma concentration; Kel = terminal elimination rate constant; Tmax = time of maximum plasma concentration; V/F = apparent volume of distribution.

* Significantly different from young subjects ($P < 0.05$). † Secondary peaks were observed in some subjects. For these subjects (n in parentheses), results for the second peak are also provided. ‡ Apparent bioavailability was computed using data from a previous investigation of intravenous fentanyl disposition in an analogous young healthy population.[44] Bioavailability was calculated as $(AUC_{0-\infty\ OTF}/Dose_{OTF})/(AUC_{0-\infty,\ IV\ fentanyl}/Dose_{IV\ fentanyl})$.

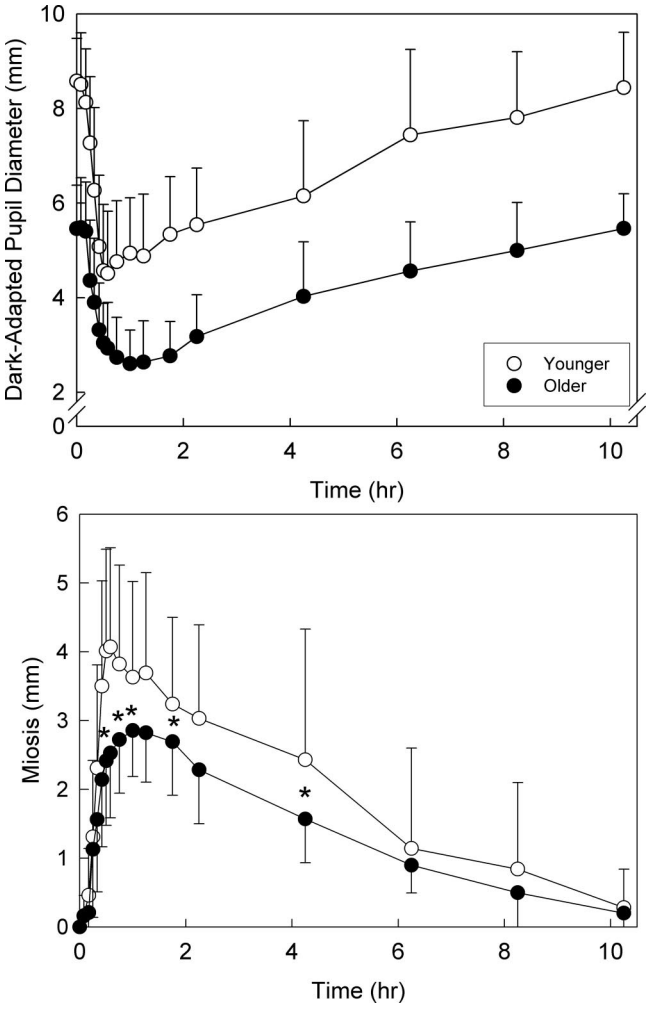

Fig. 2. Effect of age on dark-adapted pupil diameter and the pupil diameter change from baseline (miosis) after oral transmucosal fentanyl citrate. Results are mean ± SD (n = 12). Some SD are omitted for clarity.

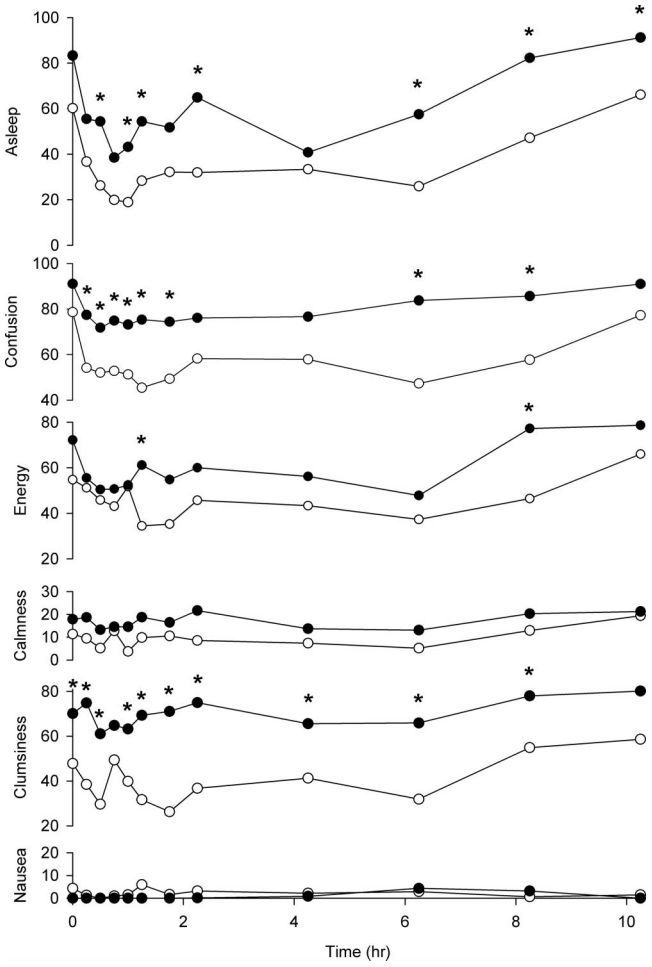

Fig. 3. Effect of age on subject self-assessment of oral transmucosal fentanyl citrate effects. Results are visual analog scores (mean ± SD, n = 12). SD are omitted for clarity. Asterisks denote significant differences between groups ($P < 0.05$). Within-group differences are not noted.

OTF disposition. The results show that when OTF is administered with careful attention to rubbing across the buccal mucosa without biting or chewing, there was no significant difference in fentanyl pharmacokinetics between healthy younger (26 ± 6 yr) and older (67 ± 6 yr) volunteers. Absorption, peak concentrations, and metabolism were not significantly changed in the older volunteers.

Table 2. Oral Transmucosal Fentanyl Effect Parameters

	Younger Subjects	Older Subjects
Maximum miosis (mm)	4.5 ± 1.1	3.1 ± 0.7*
Tmax (h)	0.79 ± 0.56	1.04 ± 0.38*
AUC_{0-10} (mm · h)	18.4 ± 11.3	13.2 ± 5.1
$AUC_{0-\infty}$ (mm · h)	22.6 ± 17.5	15.2 ± 6.9
Kel (l/h)	0.34 ± 0.17	0.27 ± 0.14
CL/F (μg/mm · h)	37.7 ± 20.6	54.4 ± 17.6
k_{e0} (h^{-1})	4.8 ± 2.8	5.0 ± 2.3

AUC_{0-10} = area under the curve of pupil diameter change (miosis) *versus* time from 0–10 h; $AUC_{0-\infty}$ = area under the curve of miosis *versus* time from time zero extrapolated to infinity; CL/F = apparent oral effect clearance; Kel = terminal effect elimination rate constant; k_{e0} = first order rate constant for transfer between plasma and the effect compartment; Tmax = time of maximum miosis.

* Significantly different from young subjects ($P < 0.05$).

There are few well-controlled investigations of fentanyl pharmacokinetics in older humans. Higher plasma concentrations were reported in older (67 ± 2 yr) *versus* younger (36 ± 4 yr) patients undergoing abdominal surgery; this has been attributed to diminished elimination clearance.[25] Volumes of distribution were reported to be age-invariant. In patients undergoing nonabdominal surgery, higher plasma concentrations in older (71–82 yr) *versus* younger (18–41 yr) patients were also reported; however, these were attributed to a lower steady-state volume of distribution, whereas elimination clearance was age-invariant.[26] In both of these investigations, however, patients received thiopental, and it has been suggested that the circulatory effects of thiopental may have influenced fentanyl disposition.[27] In another investigation of patients undergoing abdominal surgery,

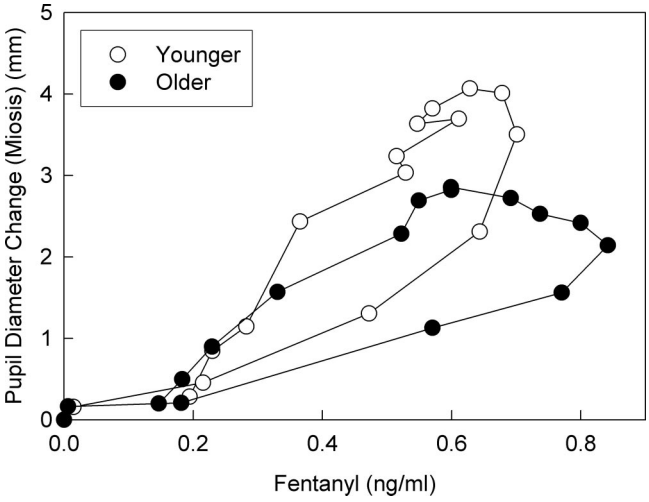

Fig. 4. Influence of age on fentanyl concentration-effect relationships after oral transmucosal fentanyl citrate shown as a hysteresis plot. Each data point is the mean of 12 subjects, with SD omitted for clarity.

there was no correlation between age (over the range 55–82 yr) and fentanyl clearance or volume of distribution.[28] Similarly, in patients receiving thiopental, there was no correlation between age (20–88 yr) and fentanyl clearances or volumes of distribution.[29] Computer simulations have also predicted that age-related changes would have only a minor influence on fentanyl pharmacokinetics.[27] In healthy volunteers not undergoing surgery, there was a greater distribution clearance in older (66 ± 3 yr) *versus* younger (24 ± 3 yr) subjects but no effect of age on systemic clearance.[30] Overall, previous investigations have not identified any consistent age-related changes in fentanyl pharmacokinetics. The current results, showing no significant effect of age on OTF kinetics, are consistent with these previous observations.

A second purpose of this investigation was to assess the effects of age on the clinical effects of OTF. The results showed a small but significantly diminished (approximately 25% less) miotic response in older volunteers. Other OTF effect measures did not appear age-related, although the investigation was not powered for this analysis. After consideration of baseline differences between younger and older subjects, visual analog scores for alertness/sedation, energy level, confusion, clumsiness, anxiety, and nausea after OTF did not appear different in the older subjects. Analgesic and respiratory effects (other than oxygen saturation) of OTF were not assessed.

The mechanism for diminished miosis in the older subjects is not apparent. It did not appear to be a result of delayed fentanyl penetration into the site of action, as the $t_{1/2}k_{e0}$ did not change with age. Indeed, the $t_{1/2}k_{e0}$ obtained in both young and old subjects (8 min) using venous concentrations was consistent with that seen previously (5–7 min) using arterial sampling.[29,31] Venous compared with arterial sampling would be expected to produce different values for $t_{1/2}k_{e0}$. Scott *et al.* also found no effect of age on $t_{1/2}k_{e0}$.[29] It is also unclear whether diminished fentanyl miosis was related to or coincident with baseline pupil diameter differences in the elderly. Dark-adapted pupil diameters were significantly smaller in the elderly subjects, consistent with the well-described age-related linear decline in pupil diameter ("senile miosis").[32–34] Resting pupil diameter reflects the balance between parasympathetically mediated cholinergic constriction and sympathetically-mediated dilation, and age-related miosis is attributed to decreased sympathetic activity.[34,35] Opioid miosis is ascribed to stimulation of the Edinger-Westphal (preganglionic parasympathetic) nucleus.[36] An age-related decline in parasympathetically-mediated miosis is not apparent, however. Pupillary responses to ocularly applied cholinergic and sympathetic agonists were unaltered and increased, respectively, with age.[35] Age-related changes in opioid effects on the Edinger-Westphal nucleus have not been reported.

The influence of age on the pharmacodynamics of fentanyl and other opioids is not entirely clear. For example, the fentanyl dose required to produce the first appearance of delta waves in a raw electroencephalogram significantly diminished with age, as did the EC_{50} (concentration producing half-maximal change) for spectral edge frequency.[29,31] There are, however, few, if any, other formal evaluations of fentanyl pharmacodynamics in the elderly. Pharmacodynamic effects of alfentanil and remifentanil were also increased significantly with age, based on the EC_{50} for spectral edge frequency changes.[29,37] In contrast, age had no effect on the pharmacodynamics of alfentanil, based on responses to intubation, skin incision, and skin closure.[38–40] The advantages and limitations of using electroencephalogram as a measure of opioid pharmacodynamics and its relationship and applicability to clinical effects have been well described.[37]

Miosis was a sensitive measure of fentanyl effect, more so than other conventional measures of opioid effect. Subnanogram venous plasma fentanyl concentrations produced profound miosis. There was no formal determination of the EC_{50} (concentration producing half-maximal change) for miosis because OTF doses were not large enough to elicit a plateau in the miotic effects. Nonetheless, it is clear from figures 1 and 2 that the EC_{50} for fentanyl miosis would clearly be in the subnanogram range. In contrast, electroencephalogram slowing occurred at approximately 3 ng/ml and the EC_{50} for spectral edge frequency was 8 ng/ml.[29] The EC_{50} for respiratory effects was 3, 3.5, and 6 ng/ml, respectively, for depression of carbon dioxide responsiveness, respiratory rate, and minute volume.[41,42] Treatment of acute pain requires 1–3 ng/ml.[43] Thus miosis is a sensitive measure of fentanyl effects, amenable to use in awake volunteers. Miosis has several advantages as an experimental measure of opioid effects, including a time course that parallels that of plasma concentrations, non-

invasiveness, objectivity, and reproducibility. Nonetheless, like the electroencephalogram, miosis is not clinical anesthesia or analgesia, and the relationship between the miotic, analgesic, respiratory, and other side effects of opioids is not well characterized. Why age decreased the miotic effects of OTF in the current investigation while increasing the electroencephalographic effects of fentanyl[29,31] requires further investigation.

Because the prevalence of pain increases with age and OTF is the only drug approved for treating breakthrough cancer pain, the current results have clinical importance. No change in OTF dosing in the elderly would appear necessary as a result of altered pharmacokinetics. No reduction in dose would appear necessary based on clinical effects, assuming that miosis is representative of analgesia and respiratory depression. Nevertheless, this is a major caveat, as the relationship between miotic, respiratory, and analgesic effects of OTF are not known. Furthermore, these conclusions are based on results with otherwise healthy elderly (61–73 yr) individuals. Effects of cancer, other concomitant illness, or older age are not known and may necessitate altered OTF dosing.

In summary, this investigation showed that in healthy older compared with younger volunteers, there were no significant differences in OTF pharmacokinetics or subjective self-assessment of effects and somewhat diminished miosis.

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References

1. Davis MP, Srivastava M: Demographics, assessment and management of pain in the elderly. Drugs Aging 2003; 20:23–57
2. Balducci L, Beghe' C: Cancer and age in the USA. Crit Rev Oncol Hematol 2001; 37:137–45
3. Levy MH: Pharmacologic treatment of cancer pain. N Engl J Med 1996; 335:1124–32
4. Portenoy RK, Lesage P: Management of cancer pain. Lancet 1999; 353: 1695–700
5. Bruera E, Kim HN: Cancer pain. JAMA 2003; 290:2476–9
6. Lawlor PG: The panorama of opioid-related cognitive dysfunction in patients with cancer: A critical literature appraisal. Cancer 2002; 94:1836–53
7. Zech DFJ, Grond S, Lynch J, Hertel D, Lehmann KA: Validation of World Health Organization Guidelines for cancer pain relief: A 10-year prospective study. Pain 1995; 63:65–76
8. Portenoy RK, Payne D, Jacobsen P: Breakthrough pain: Characteristics and impact in patients with cancer pain. Pain 1999; 81:129–34
9. Mercadante S, Radbruch L, Caraceni A, Cherny N, Kaasa S, Nauck F, Ripamonti C, De Conno F: Episodic (breakthrough) pain: Consensus conference of an expert working group of the European Association for Palliative Care. Cancer 2002; 94:832–9
10. Fortner BV, Okon TA, Portenoy RK: A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain. J Pain 2002; 3:38–44
11. Stanley TH, Hague B, Mock D, Streisand JB, Bubbers S, Dzelzkalns RR, Bailey PL, Pace NL, East KA, Ashburn MA: Oral transmucosal fentanyl citrate (lollipop) premedication in human volunteers. Anesth Analg 1989; 69:21–7
12. Fine PG, Marcus M, Just De Boer A, Van der Oord B: An open label study of oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough cancer pain. Pain 1991; 45:149–53
13. Farrar JT, Cleary J, Rauck R, Busch M, Nordbrock E: Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo- controlled trial for treatment of breakthrough pain in cancer patients. J Natl Cancer Inst 1998; 90:611–616
14. Christie JM, Simmonds M, Patt R, Coluzzi P, Busch MA, Nordbrock E, Portenoy RK: Dose-titration, multicenter study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. J Clin Oncol 1998; 16:3238–45
15. Portenoy RK, Payne R, Coluzzi P, Raschko JW, Lyss A, Busch MA, Frigerio V, Ingham J, Loseth DB, Nordbrock E, Rhiner M: Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: A controlled dose titration study. Pain 1999; 79:303–12
16. Payne R, Coluzzi P, Hart L, Simmonds M, Lyss A, Rauck R, Berris R, Busch MA, Nordbrook E, Loseth DB, Portenoy RK: Long-term safety of oral transmucosal fentanyl citrate for breakthrough cancer pain. J Pain Symptom Manage 2001; 22:575–83
17. Coluzzi PH, Schwartzberg L, Conroy JD, Charapata S, Gay M, Busch MA, Chavez J, Ashley J, Lebo D, McCracken M, Portenoy RK: Breakthrough cancer pain: A randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). Pain 2001; 91:123–30
18. Streisand JB, Varvel JR, Stanski DR, Le Maire L, Ashburn MA, Hague BI, Mock D, Tarver SD, Stanley TH: Absorption and bioavailability of oral transmucosal fentanyl citrate. ANESTHESIOLOGY 1991; 75:223–9
19. Streisand JB, Busch MA, Egan TD, Smith BG, Gay M, Pace NL: Dose proportionality and pharmacokinetics of oral transmucosal fentanyl citrate. ANESTHESIOLOGY 1998; 88:305–9
20. Egan TD, Sharma A, Ashburn MA, Kievit J, Pace NL, Streisand JB: Multiple dose pharmacokinetics of oral transmucosal fentanyl citrate in healthy volunteers. ANESTHESIOLOGY 2000; 92:665–73
21. Lee M, Kern SE, Kisicki JC, Egan TD: A pharmacokinetic study to compare two simultaneous 400 μg doses with a single 800 μg dose of oral transmucosal fentanyl citrate. J Pain Symptom Manage 2003; 26:743–7
22. Kharasch ED, Whittington D, Hoffer C: Influence of hepatic and intestinal cytochrome P4503A activity on the acute disposition and effects of oral transmucosal fentanyl citrate. ANESTHESIOLOGY 2004; 101:729–37
23. Phimmasone S, Kharasch ED: A pilot evaluation of alfentanil-induced miosis as a noninvasive probe for hepatic cytochrome P450 3A4 (CYP3A4) activity in humans. Clin Pharmacol Ther 2001; 70:505–17
24. Fuseau E, Sheiner LB: Simultaneous modeling of pharmacokinetics and pharmacodynamics with a nonparametric pharmacodynamic model. Clin Pharmacol Ther 1984; 35:733–41
25. Bentley JB, Borel JD, Nenad REJ, Gillespie TJ: Age and fentanyl pharmacokinetics. Anesth Analg 1982; 61:968–71
26. Singleton MA, Rosen JI, Fisher DM: Pharmacokinetics of fentanyl in the elderly. Br J Anaesth 1988; 60:619–22
27. Björkman S, Wada DR, Stanski DR: Application of physiologic models to predict the influence of changes in body composition and blood flows on the pharmacokinetics of fentanyl and alfentanil in patients. ANESTHESIOLOGY 1998; 88:657–67
28. Hudson RJ, Thomson IR, Cannon JE, Friesen RM, Meatherall RC: Pharmacokinetics of fentanyl in patients undergoing abdominal aortic surgery. ANESTHESIOLOGY 1986; 64:334–8
29. Scott JC, Stanski DR: Decreased fentanyl and alfentanil dose requirements with age: A simultaneous pharmacokinetic and pharmacodynamic evaluation. J Pharmacol Exp Ther 1987; 240:159–66
30. Ariano RE, Duke PC, Sitar DS: Population pharmacokinetics of fentanyl in healthy volunteers. J Clin Pharmacol 2001; 41:757–63
31. Scott JC, Cooke JE, Stanski DR: Electroencephalographic quantitation of opioid effect: Comparative pharmacodynamics of fentanyl and sufentanil. ANESTHESIOLOGY 1991; 74:34–42
32. Birren JE, Casperson RC, Botwinick J: Age changes in pupil size. J Gerontol 1950; 5:216–21
33. Winn B, Whitaker D, Elliott DB, Phillips NJ: Factors affecting light-adapted pupil size in normal human subjects. Invest Ophthalmol Vis Sci 1994; 35:1132–7
34. Bitsios P, Prettyman R, Szabadi E: Changes in autonomic function with age: A study of pupillary kinetics in healthy young and old people. Age Ageing 1996; 25:432–8
35. Davis PB, Byard PJ: Relationships among airway reactivity, pupillary α-adrenergic and cholinergic responsiveness, and age. J Appl Physiol 1988; 65:200–4
36. Murray RB, Adler MW, Korczyn AD: The pupillary effects of opioids. Life Sci 1983; 33:495–509
37. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJM, Gambus PL, Billard V, Hoke JF, Moore KHP, Hermann DJ, Muir KT, Mandema JW, Shafer SL: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. ANESTHESIOLOGY 1997; 86:10–23
38. Ausems ME, Hug CC, Stanski DR, Burm AGL: Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. ANESTHESIOLOGY 1986; 65:362–73
39. Lemmens HJM, Bovill JG, Hennis PJ, Burm AGL: Age has no effect on the pharmacodynamics of alfentanil. Anesth Analg 1988; 67:956–60
40. Lemmens HJ, Burm AG, Bovill JG, Hennis PJ: Pharmacodynamics of alfentanil as a supplement to nitrous oxide anaesthesia in the elderly patient. Br J Anaesth 1988; 61:173–9
41. Cartwright P, Prys-Roberts C, Gill K, Dye A, Stafford M, Gray A: Ventilatory depression related to plasma fentanyl concentrations during and after anesthesia in humans. Anesth Analg 1983; 62:966–74
42. Mildh LH, Scheinin H, Kirvela OA: The concentration-effect relationship of the respiratory depressant effects of alfentanil and fentanyl. Anesth Analg 2001; 93:939–46
43. Peng PWH, Sandler AN: A review of the use of fentanyl analgesia in the management of acute pain in adults. ANESTHESIOLOGY 1999; 90:576–99
44. Ibrahim AE, Feldman J, Karim A, Kharasch ED: Simultaneous assessment of drug interactions with low- and high-extraction opioids: Application to parecoxib effects on the pharmacokinetics and pharmacodynamics of fentanyl and alfentanil. ANESTHESIOLOGY 2003; 98:853–61