PHARMACOKINETICS OF FENTANYL IN THE ELDERLY

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Elderly patients are believed to be more sensitive to the depressant effects of opioid drugs [1]. This increase in sensitivity may result from age-related changes in either the pharmacokinetics or the pharmacodynamics of the opioids. One possible explanation is that changes in organ function and structure (such as the increase in fat as a percentage of body weight or the decrease in hepatic blood flow) alter the distribution or elimination of such drugs. Another possibility is that changes in the central nervous system alter sensitivity to opioids. To determine whether the distribution or elimination of fentanyl is affected by age-related changes in organ function and structure, we compared the pharmacokinetics of fentanyl in elderly and young adults.

PATIENTS AND METHODS

After obtaining approval from our Committee on Human Research and informed consent from patients, we studied seven elderly (71-82 yr, three males) and seven younger adults (18-41 yr, four males), ASA class I or II. All patients were unpremedicated and undergoing elective non-abdominal surgery. Anaesthesia was induced with thiopentone 2-6 mg kg$^{-1}$ and maintained with 60% nitrous oxide in oxygen. Pancuronium was administered and ventilation controlled to maintain end-tidal $P_{\text{CO}_2}$ at 4.7-5.3 kPa. Nasopharyngeal temperature was maintained at 35-37 °C. After the induction of anaesthesia, fentanyl was administered as a 2-min i.v. infusion at doses of 15 μg kg$^{-1}$ for elderly patients and 20 μg kg$^{-1}$ for the younger patients. A smaller dose of fentanyl was administered to the elderly patients because we were concerned that larger doses might not be tolerated clinically. Arterial plasma samples were obtained before infusion, and at 1, 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min after the start of infusion. Plasma fentanyl concentrations were determined by radioimmunoassay [2, 3], sensitive to 0.5 ng ml$^{-1}$ [4] and having a coefficient of variation of 10% at a concentration of 1.0 ng ml$^{-1}$. Non-compartmental techniques [5] were used to determine the following pharmacokinetic variables: elimination half-life ($T_{\text{1/2}}$); total plasma clearance ($C_l$); volume of distribution at steady-state ($V_{\text{Dss}}$);

SUMMARY

The pharmacokinetics of fentanyl were determined in seven elderly (71-82 yr) and seven younger adults (18-41 yr) anaesthetized with thiopentone, nitrous oxide in oxygen and morphine. Fentanyl was administered as a 2-min i.v. infusion at doses of 15 μg kg$^{-1}$ for elderly patients and 20 μg kg$^{-1}$ for the younger patients. Plasma samples were obtained for 4 h and fentanyl concentrations determined by radioimmunoassay. Fentanyl concentration, per μg kg$^{-1}$ administered, was higher in elderly than in young patients at 2 min (7.73±3.14 v. 4.54±1.93 ng ml$^{-1}$ (mean±SD), respectively) and at 4 min after the start of infusion (3.26±1.44 v. 1.76±0.72 ng ml$^{-1}$, respectively). Concentrations were similar at all other sampling times. Pharmacokinetic variables were determined by non-compartmental techniques. Total plasma clearance was similar for the two age groups. Volume of distribution at steady-state ($V_{\text{Dss}}$) was smaller in elderly patients (1.36±0.44 v. 2.27±0.82 litre kg$^{-1}$). Despite age-related changes in $V_{\text{Dss}}$, plasma fentanyl concentrations for the two groups were similar throughout the 4-h sampling period except immediately following administration. These results suggest that, if there are age-related differences in response to fentanyl, the likely pharmacokinetic explanation is the higher concentration of fentanyl in the elderly immediately following its administration.


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mean residence time ($V_{DSS}/Cl$). In addition, for each patient, we calculated the plasma concentration of fentanyl per $\mu$g kg$^{-1}$ administered at each sampling time. Mean values for the two age groups were compared using Student’s $t$ test for unpaired data [6]; $P < 0.05$ was considered significant.

Fentanyl concentration per $\mu$g kg$^{-1}$ administered was higher in the elderly than in the younger patients at 2 min ($7.73 \pm 3.14$ vs. $4.54 \pm 1.83$ ng ml$^{-1}$ (mean ± SD), respectively) and at 4 min after the start of infusion ($3.26 \pm 1.44$ vs. $1.78 \pm 0.72$ ng ml$^{-1}$, respectively) (fig. 1). Concentrations at all other sampling times were similar for both age groups (figs 1, 2).

Elderly patients had a smaller volume of distribution at steady-state compared with young patients (table I). There were no differences in $T_1^\beta$, $Cl$ or mean residence time.

**DISCUSSION**

If the elderly are more sensitive to the depressant effects of opioids [1], age-related changes in the pharmacokinetics or pharmacodynamics of such
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drugs could be the explanation. In this study, we found that the pharmacokinetics of fentanyl were similar for elderly and young patients, except for a smaller volume of distribution at steady-state in the elderly. In addition, following the administration of weight-normalized doses, plasma fentanyl concentrations were similar at all times except in the period immediately following administration. Consequently, during recovery from anaesthesia; that is 120–240 min after fentanyl administration, plasma fentanyl concentrations were similar in both groups.

Physiological changes associated with ageing would be expected to influence the metabolism and distribution of fentanyl. For example, ageing decreases liver blood flow [7]. Since most of the fentanyl entering the hepatic circulation is metabolized, this decrease in liver blood flow should decrease the clearance of fentanyl. However, we found no age-related decrease in Cl. Our finding is similar to that for lignocaine [8], another drug highly extracted by the liver, and may reflect our selection of healthy elderly subjects.

Another age-related change is a decrease in lean body mass and an increase in fat as a percentage of body weight [9]. For lipophilic drugs such as fentanyl, this should increase the volume of distribution at steady-state. In contrast, we found that VDss for fentanyl was smaller in the elderly group. The VDss for another lipophilic drug, thiopentone, is similar in young and elderly subjects [10]. Thus, ageing does not necessarily increase the VDss of lipophilic drugs.

Ageing is also associated with the decrease in the volume of extracellular fluid as well as a decrease in blood flow to organs in the vessel-rich group [10]. These factors may limit the distribution of fentanyl from blood, resulting in a higher initial plasma concentration, and would explain the higher concentration of fentanyl observed in our elderly patients immediately after administration. This higher initial concentration has also been observed with thiopentone [10] and may explain the greater response of the elderly to weight-normalized doses of that drug [10]. In support of this, Homer and Stanski [10] have demonstrated that the steady-state plasma concentrations of thiopentone that produce the same degree of electroencephalographic depression are similar in young and elderly subjects. Thus, the greater response of the elderly to weight-normalized doses of thiopentone is the result of pharmacokinetic changes; that is, a higher initial plasma concentration and, because thiopentone enters the brain rapidly, presumably a higher initial brain concentration.

Fentanyl also enters the brain rapidly [11]. Consequently, higher peak plasma concentrations of fentanyl in elderly patients may result in a greater peak response, such as depression of ventilation. Within 10 min of administration of weight-normalized doses, plasma fentanyl concentrations were similar in elderly and young patients. Thus, pharmacokinetic differences could explain only differences in peak response, and not differences occurring 1–4 h after administration.

Ageing may also produce pharmacodynamic changes that explain the more profound response of elderly patients to opioids. These pharmacodynamic changes may involve either differences in drug concentrations in the brain (for example, if there were less protein binding of fentanyl in the elderly) or differences in the sensitivity of the brain. Changes in the ventilatory response with ageing have been investigated in two studies. Arunsalam and colleagues [12] obtained ventilatory measurements before and after the i.v. administration of morphine 10 mg/70 kg, to young and elderly subjects. The decreases in minute ventilation and ventilatory frequency and the increase in end-tidal PCO2 were comparable for both. However, more than half of the elderly subjects had significant episodes of apnoea or periodic breathing. In contrast, apnoea or periodic breathing occurred in fewer than 25% of the young subjects and with a lower frequency. These results suggest that, for a comparable pharmacodynamic endpoint (increase in Pco2 or decrease in minute ventilation), elderly subjects differ from young subjects in ventilatory pattern in response to morphine.

Peterson and co-workers [13] found that ventilatory responses to hyperoxic hypercapnia and isocapnic hypoxia were blunted approximately 50% in elderly subjects. These decreases in ventilatory response were proportional to an age-related decrease in occlusion pressure response (the inspiratory pressure generated 100 ms after airway occlusion). Peterson and co-workers [13] concluded that the difference in the pattern of ventilation resulted from age-related changes in neuromuscular, rather than central nervous system, function.

In combination, these two studies suggest that the ventilatory response of the elderly differs both in the presence [12] and absence [13] of opioids.
Our findings differ from those of Bentley and colleagues [14] who compared the pharmacokinetics of fentanyl in four elderly women (mean age 67 yr; range 61–73 yr) and five young women (mean age 36 yr; range 29–49 yr). They found that the volume of distribution was similar for elderly and young patients (4.9 ± 0.5 and 5.9 ± 0.8 litre kg⁻¹ (mean ± SEM), respectively) and that Cl was decreased markedly in the elderly patients (4.0 ± 0.6 vs. 15.4 ± 1.6 ml kg⁻¹ min⁻¹). They obtained samples for 7 h (in contrast to 4 h in our study), and determined fentanyl concentrations by gas chromatography. Their anaesthetic technique (nitrous oxide, thiopentone and controlled ventilation) was similar to ours. Two differences in study design may explain the difference in results. First, Bentley and colleagues [14] did not measure Pco₂. This is important because hyper-ventilation, and the attendant hypocarbia, are known to decrease clearance of fentanyl [15]. Second, all of their subjects (and none of ours) underwent abdominal surgery, which produces a significant decrease in hepatic blood flow [16] that may alter the clearance of fentanyl.

In summary, we found that the clearance of fentanyl was similar in elderly and younger patients, and Vbss smaller in elderly patients. Plasma concentration of fentanyl was higher in the elderly patients immediately after administration, but similar for the two age groups during the subsequent 4 h. Our results suggest that if the effects of fentanyl are more pronounced in elderly subjects, the likely pharmacokinetic explanation is the higher initial concentration.

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REFERENCES