Comparison of intravenous and intranasal sufentanil absorption and sedation

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The absorption and sedation following an intranasal dose of sufentanil were evaluated and compared with those of the same dose given intravenously. Sixteen adult patients scheduled for elective surgery were randomly allocated to receive as premedication 15 μg sufentanil either intravenously or intranasally. Before administration and at fixed time intervals thereafter, the degree of sedation was assessed, vital signs were recorded and venous blood samples were taken for the determination of sufentanil plasma concentrations. Peroperative sedation of rapid onset and limited duration was seen in both groups. However, the onset of sedation was more rapid after intravenous injection. At 10 min, all patients in the IV group were sedated versus only two in the intranasal group ($P < 0.01$). No significant intergroup differences in sedation were seen at 20 to 60 min. This clinical effect is in agreement with the measured plasma levels, which were significantly lower after intranasal application at 5 and 10 min, being 36 and 56 per cent of those after IV dosing, respectively. From 30 min, plasma concentrations were virtually identical for the two routes of administration. The $AUC_{0\text{-}120\ min}$ after intranasal dosing was 78 per cent of that after intravenous injection. Intranasal dosing induced no clinically significant changes in vital signs, whereas after IV sufentanil, a clinically significant decrease in PaO_2 was seen at 5 min. The results of this study show that sufentanil, when administered intranasally, is rapidly and effectively absorbed from the human nasal mucosa, so that this route may be an attractive alternative for a premedicant, avoiding the discomfort of an intravenous or intramuscular injection.

Key words
ANALGESICS: sufentanil; PREMEDICATION: sufentanil; route of administration: intravenous, intranasal; PHARMACOKINETICS: absorption.

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The intranasal route has been shown to be a very useful alternative for drugs for which, hitherto, only parenteral administration has been possible.[1] The efficacy of intranasal midazolam as a preoperative sedative[2] and of intranasal sufentanil as a pre-induction agent[3] has recently been demonstrated in children.

In adults sufentanil, given intranasally one hour before surgery, rapidly produces effective preoperative sedation of limited duration.[4] The *in vitro* effects of sufentanil on ciliary movement of human nasal epithelial tissue have been shown to be minimal and certainly no impediment to nasal administration.[5] However, a critical variable in the consideration of intranasal administration of sufentanil is systemic absorption. Therefore, we decided to measure sufentanil plasma concentrations after intranasal and intravenous administration of "low-dose" sufentanil and to compare the respective clinical effects. We chose the intravenous route so as to provide an exact reference with respect to the bioavailability of the intranasal formulation.

Methods

Sixteen consenting adult patients ASA physical status I and II, scheduled for elective surgery (mainly arthroscopy) were admitted to the study (Table I). They were randomly allocated to receive either intranasal or intravenous sufentanil (15 μg), one hour before surgery. Nine patients received three drops of 2.5 μg in each nostril while in the supine position with the head tilted back, and seven received IV sufentanil over a 30-sec period. Before administration and at 10, 20, 40 and 60 min thereafter, an experienced recovery-room nurse assessed the degree of sedation, using a 4-point scale: 0 = absent (patient alert); 1 = slight (patient drowsy, but oriented and initiates conversation); 2 = moderate (patient drowsy; still oriented but does not initiate conversation); 3 = marked (patient very drowsy; when undisturbed, falls asleep). At the same

TABLE I Patient data (mean and range)

	Sufentanil IV $n = 7$	*Sufentanil intranasal* $n = 9$
Age yr	36(24–46)	27(24–40)
Weight kg	71(65–76)	71(56–86)
Sex		
Female	6	4
Male	1	5

time, blood pressure and heart rate were recorded by means of an invasive blood-pressure monitor (Siemens Sirecust 2000), and the respiratory rate was recorded by a nurse. Arterial blood gas analyses were performed before and at 5, 10, 30 and 60 min after dosing.

Venous blood was sampled before and at 5, 10, 30, 60 and 120 minutes after dosing. Sufentanil plasma concentrations were determined by a radio immuno-assay with a detection limit of 0.01 ng · ml^{-1}.[6] Areas under the plasma concentration-time curve of sufentanil from 0 min to 120 min after dosing ($AUC_{0\text{-}120\ min}$) were calculated by trapezoidal summation. Intergroup differences were statistically analysed with the Mann-Whitney U test and intragroup changes from baseline with the Wilcoxon test. Differences were considered significant when the two-tailed probability was less than 0.05.

Results

Pharmacokinetics

Mean sufentanil plasma concentrations after 15 μg intranasal and IV administration are shown in the Figure. After intranasal dosing, maximal concentrations of 0.080 ± 0.029 ng · ml^{-1} were reached after 10 min. During absorption from the nose, sufentanil concentrations at 5 and 10 min were 36 and 56 per cent of those after IV dosing, respectively. At 30, 60 and 120 min, there were no significant differences between the sufentanil concentrations of the two dosing routes. The $AUC_{0\text{-}120\ min}$ after intranasal dosing was 78 per cent of that after IV injection (mean ± SEM: 5.75 ± 0.53 ng · min · ml^{-1} versus 7.36 ± 0.33 ng · min · ml^{-1} $P < 0.05$).

Sedation

The onset of preoperative sedation was rapid after IV sufentanil: all patients were sedated beginning at 10 min ($P = 0.02$, Wilcoxon test). The peak effect occurred at 20 min. At 60 min, sedation was absent or mild in four patients. In the intranasal group, only two patients were sedated at 10 min (P = NS). The effect was significant at 20 min ($P = 0.02$) and peaked at 40 min ($P < 0.01$). At 60 min, sedation was absent or mild in five of the patients.

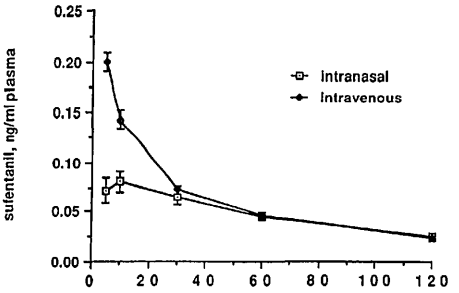

FIGURE *Mean* (±SEM) plasma concentrations after 15 μg intranasal (n = 9) and intravenous (n = 7) sufentanil.

TABLE II Sedation score (mean ± SEM)

Min after dosing	*Suf. IV* $n = 7$	*Suf. intranasal* $n = 9$	*IV vs intranasal*
0	0	0	NS
10	1.4 ± 0.2*	0.3 ± 0.2	$P < 0.01$
20	2.0 ± 0.3*	1.2 ± 0.3*	NS
40	1.7 ± 0.4	2.1 ± 0.3†	NS
60	1.2 ± 0.5	1.6 ± 0.3†	NS

*$P < 0.05$ (compared with control value).
†$P < 0.01$ (compared with control value).

The intergroup difference in onset of action was significant ($P < 0.01$ at 10 min, Mann-Whitney U test). Although the effect after intranasal administration was not yet full-blown at 20 min, and that of the IV injection had worn off somewhat more markedly by 60 min, intergroup differences at 20 to 60 min were not significant (Table II).

Vital signs

Cardiovascular variables remained stable throughout the observation period, with no intergroup differences (Table III). Respiratory rate decreased significantly at 10, 20 and 40 min after IV sufentanil and at 10 and 40 min after intranasal application. A respiratory rate below 10 · min^{-1} was not observed in any patient. No significant intergroup differences were seen (Table IV). The arterial glood gas analyses showed statistically significant changes after IV sufentanil; the only clinically relevant change was the PaO_2 decrease at 5 min. After intranasal dosing, no statistically or clinically significant changes were observed. As a consequence, significant differences between IV and intranasal sufentanil were seen in pH, PaO_2 and S_aO_2 (Table V).

TABLE III Cardiovascular variables (mean ± SEM)

Min after dosing	*Sufentanil IV n = 7*	*Sufentanil intranasal n = 9*
Systolic blood pressure (mmHg)		
0	141 ± 5	143 ± 5
10	131 ± 5	144 ± 5
20	135 ± 6	143 ± 6
40	125 ± 5	136 ± 7
60	126 ± 9	139 ± 7
Diastolic blood pressure (mmHg)		
0	74 ± 3	74 ± 3
10	77 ± 4	77 ± 3
20	80 ± 4*	75 ± 3
40	73 ± 4	76 ± 6
60	75 ± 3	77 ± 3
Heart rate (bpm)		
0	82 ± 10	76 ± 4
10	79 ± 8	77 ± 4
20	82 ± 8	79 ± 4
40	76 ± 9	72 ± 2
60	83 ± 10	74 ± 3

*$P < 0.05$ (Student's t test, two-paired.

Acceptability

Dizziness was the only drug-related side-effect and was reported by three of the nine patients receiving intranasal sufentanil and by four of the seven receiving IV sufentanil. All patients in both groups experienced the sedative effect of sufentanil, and all (including those who complained of dizziness) stated they would have no objection to receiving it again in a similar situation.

Discussion

Oral drug administration, although convenient, is often not effective because of extensive first-pass metabolism or poor stability in gastro-intestinal fluids. The parenteral route can be used but has the disadvantage of causing discomfort in the awake patient. The reason for administering premedication in the first place is to provide comfort and render anaesthesia and surgery less traumatic. The results of this and other recent work[3,4] suggest that the intranasal route is an alternative mode of administration for sufentanil. Effective preoperative sedation of rapid onset and limited duration, but producing some dizziness was observed in this study. The plasma concentrations after intranasal sufentanil indicate rapid and effective absorption from the human nasal mucosa. The only difference between the two routes occurs in the first ten minutes during which peak plasma concentrations after intranasal application are significantly lower, thus reducing the risk of early side-effects. After thirty minutes, the plasma concentration time profile is virtually identical to that after IV sufentanil. Intranasal dosing had no effect on vital signs. Future studies using more sensitive methods of evaluating respiratory function, e.g., a CO_2 dose–response curve and containing larger numbers of patients, are needed to confirm the present data. In conclusion, intranasally administered sufentanil

TABLE IV Respiratory rate (mean ± SEM)

Min after dosing	*Sufentanil IV n = 7*	*Sufentanil intranasal n = 9*
0	*15.6* ± 0.2	15.4 ± 0.7
10	11.9 ± 0.5*	13.0 ± 0.7*
20	12.7 ± 0.5*	13.8 ± 0.7
40	13.2 ± 0.7*	13.6 ± 0.3*
60	14.3 ± 0.6	14.1 ± 0.5

*$P < 0.05$ (Student's t test).

TABLE V Arterial blood gas analyses (mean ± SEM)

Time	*Suf. IV*	*Suf. intranasal*	*IV vs intranasal*
pH			
0	7.37 ± 0.01	7.38 ± 0.01	NS
5	7.34 ± 0.01	7.37 ± 0.01	< 0.05
10	7.34 ± 0.02	7.39 ± 0.02	NS
30	7.34 ± 0.01*	7.37 ± 0.02	NS
60	7.36 ± 0.02	7.38 ± 0.01	NS
$PaCO_2$ (mmHg)			
0	36.4 ± 1.0	38.4 ± 1.0	NS
5	41.3 ± 0.9*	38.9 ± 0.7	NS
10	40.6 ± 1.3*	38.7 ± 0.7	NS
30	41.4 ± 1.1*	39.0 ± 1.5	NS
60	39.6 ± 2.0	37.8 ± 1.2	NS
(HCO_3-) (mmol/L)			
0	21.0 ± 0.6	22.6 ± 0.6	NS
5	22.4 ± 0.5*	22.7 ± 0.6	NS
10	21.9 ± 0.6*	22.6 ± 0.4	NS
30	22.1 ± 0.7*	22.8 ± 0.5	NS
60	22.8 ± 0.7	22.8 ± 0.5	NS
PaO_2 (mmHg)			
0	89.7 ± 5.2	92.8 ± 3.4	NS
5	71.7 ± 3.9*	94.8 ± 3.5	< 0.005
10	80.4 ± 3.2	96.8 ± 3.1	< 0.05
30	84.1 ± 4.9	100.6 ± 4.2	< 0.05
60	87.3 ± 5.0	99.1 ± 5.2	NS
SaO_2 (%)			
0	96.4 ± 0.6	96.8 ± 0.3	NS
5	92.6 ± 1.4	97.0 ± 0.3	< 0.005
10	95.0 ± 0.6	97.1 ± 0.4	< 0.01
30	95.1 ± 0.7	97.6 ± 0.4	< 0.05
60	96.6 ± 1.0	97.7 ± 0.6	NS

*$P < 0.05$ compared with control value (Student's (t test).

is rapidly and effectively absorbed and may be an attractive alternative as a preoperative premedicant.

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Résumé

Nous avons comparé les voies intraveineuse et intranasale quant à l'absorption du sufentanil et à la sédation produite. Ainsi, en pré-opératoire d'interventions électives, 16 adultes randomisés ont reçu 15 mcg de sufentanil par voie veineuse ou nasale. Nous avons évalué l'effet sédatif, mesuré les signes vitaux et les niveaux sériques de sufentanil avant et à intervalle régulier après la prise du médicament. Un effet sédatif de courte durée est apparu rapidement avec le mode nasal alors que par mode vieneux, ce même effet survenait de façon encore plus précoce. En fait, à dix minutes, il y avait sédation chez tous les patients du groupe veineux contre seulement deux patients du groupe nasal ($P < 0,01$) alors qu'à 20 et 60 minutes, les deux groupes étaient comparables. L'effet sédatif peut être mis en parallèle avec les niveaux sériques de sufentanil qui à cinq et dix minutes post-instillation nasale n'atteignaient respectivement que 36 et 56 pour cent de ceux observé post-injection. A partir de 30 minutes, les niveaux sériques des deux groupes étaient pratiquement indentiques. Entre 0 et 120 minutes, l'aire sous la courbe des niveaux sériques ($AUC_{0\text{-}120}$) atteints par voie nasale équivalait à 78 pour cent de celle produite par voie veineuse. Cinq minutes post-sufentanil IV, nous avons observé une baisse significative de la PaO_2 tandis que par voie nasale, les signes vitaux demeuraient inchangés. Ainsi, chez l'humain, la muqueuse nasale absorbe rapidement le sufentanil et présente donc une alternative à l'injection intraveineuse ou intramusculaire de la prémédication.