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Pharmacokinetics and ventilatory effects of intravenous oxycodone in postoperative children

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1 Oxycodone hydrochloride (0.1 mg kg^{-1}) was given by intravenous bolus to 18 children after ophthalmic surgery. Plasma was sampled for up to 8 h. Blood pressure, heart rate, peripheral arteriolar oxygen saturation, end-tidal carbon dioxide and halothane concentrations and ventilatory rate were also recorded.

2 Mean (±s.d.) values of drug clearance and volume of distribution (V_{ss}) were 15.2 ± 4.2 ml min^{-1} kg^{-1} and 2.1 ± 0.8 l kg^{-1}. Maximum mean end-tidal carbon dioxide concentration and minimum mean ventilatory rate occurred 8 min after administration of oxycodone but the minimum mean peripheral arteriolar oxygen saturation occurred at 4 min.

3 Oxycodone (0.1 mg kg^{-1}) appears to cause greater ventilatory depression than comparable analgesic doses of other opioids.

Keywords oxycodone ventilation pharmacokinetics pharmacokinetic-dynamic models

Introduction

In Finland oxycodone is the opioid analgesic most commonly used for adult postoperative pain [1]. According to textbooks of anaesthesia, 15 mg of intramuscular oxycodone is equianalgesic to 10 mg of intramuscular morphine [2,3]. However, in a recent study with adult patients oxycodone provided postoperative analgesia more rapidly and with smaller doses than did morphine. Oxycodone has a longer duration of action than morphine and it has been shown to be effective after oral administration for cancer pain [1,4]. Its use in children is also increasing, although its analgesic efficacy has not been studied in paediatric patients. The pharmacokinetics of oxycodone have been reported only in adults [5-7]. We have studied the pharmacokinetics and ventilatory effects of oxycodone given intravenously to children after ophthalmic surgery.

Methods

Subjects and protocol

We obtained informed consent from the parents and institutional approval to study 18 healthy, ASA physical status 1 children, aged 2-10 years, scheduled for extraocular muscle surgery. Preanaesthetic medication consisted of 0.1 mg kg^{-1} (maximum 2 mg) of oral liquid flunitrazepam. An intravenous infusion of 5% w/v glucose in 0.3% w/v saline was started at a rate of 10 ml kg^{-1} h^{-1} for the first hour and continued at 2.5 ml kg^{-1} h^{-1} until the end of the study. Anaesthesia was induced with thiopentone (5 mg kg^{-1}), and muscle relaxation was achieved with pancuronium (0.1 mg kg^{-1}). Following tracheal intubation, the lungs were ventilated mechanically using a Siemens Elema 900 ventilator (Siemens, Sweden). Anaesthesia was maintained with nitrous oxide in 30% oxygen and halothane (1–2 vol%). The degree of neuromuscular blockade was monitored with a transcutaneous nerve stimulator. At the end of anaesthesia residual neuromuscular blockade was antagonized with neostigmine and glycopyrrolate. During anaesthesia an anaesthetic cream (EMLA® Astra, Sweden) was applied to the patient's nostrils to facilitate the postoperative measurement of end-tidal gas flow. At the end of anaesthesia, the nose and pharynx were cleared with suction to ensure free air flow and a small plastic tube was inserted in one of the patient's nostrils to collect end-tidal gas samples. No blood was lost postoperatively.

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After transfer to the recovery room patients were positioned to their side and were given additional oxygen for 20 min, and continuous monitoring was started. Blood pressure, heart rate and peripheral arteriolar oxygen saturation (SpO_2) were monitored with a Cardiocap CMO (Datex, Finland). End-tidal carbon dioxide ($ETCO_2$), halothane concentrations and ventilatory rate were monitored with a Capnomac (Datex, Finland). Blood pressure was measured every 5 min and the other variables as a mean of measurements taken every 10 s. Measurements were continued until the patients no longer tolerated the plastic sampling tube in the nostril, usually about 3 h.

Thirty minutes after discontinuation of anaesthesia and 10 min after discontinuation of additional oxygen, a single intravenous dose of 0.1 mg kg^{-1} of oxycodone hydrochloride was given for prophylactic analgesia through a cannula inserted in a foot vein. At 2, 5, 10, 15, 30, 60, 120, 180, 240 min, and 6 to 8 h after administration of oxycodone blood samples (1.5 ml) were drawn for oxycodone assay from a cannula inserted in a hand vein. A total of 15 to 16.5 ml blood (less than 2 % of the patient's blood volume) was collected. Plasma was separated, frozen immediately and stored at -20°C until assay by gas chromatography [8]. The lower limit of determination of the method was 3 ng ml^{-1} and the intra-day coefficient of variation was 7% (52 ng ml^{-1}, n=10).

Postoperative pain over the first 3 h was assessed by a trained observer [9]. If the patient was assessed to have pain during the observation period (pain score $\geq$ 2), intravenous diclofenac (1 mg kg^{-1}) was given as indicated clinically as a rescue analgesic. Because the patients were mostly asleep during the study and because no major pain was expected after ophthalmic surgery, pain scores are not reported. All side-effects and adverse reactions were recorded. Patients were given additional oxygen or ventilation was assisted manually if SpO_2 decreased to less than 90% and did not improve in 20 s or ventilatory rate decreased below 8 per min. Additional oxygen was removed when ventilation appeared to be sufficient. If additional oxygen was given, SpO_2 values were excluded from the data analysis for the duration of oxygen administration and 2 min thereafter. Correspondingly, if the patients lungs were ventilated manually, SpO_2 and $ETCO_2$ values were excluded from the data analysis for the duration of ventilation and 2 min thereafter.

Pharmacokinetic analysis

Plasma drug concentrations were fitted by a multiexponential function using iteratively reweighted non-linear least squares regression with reciprocal squared prediction weighting [10]. The goodness of the fit was determined by Akaike's information criterion [11] and by assessment of the weighted residuals. Initial and terminal half-lives ($t_{1/2,1}$) and ($t_{1/2,z}$), initial volume of distribution (V_1), steady-state volume of distribution (V_{ss}) and clearance (CL) were calculated [12].

Relation of plasma concentrations of oxycodone and end-tidal halothane concentrations to ventilation

Because both opioids [13] and volatile anaesthetics [14] affect ventilation, oxycodone and halothane concentrations and changes in end-tidal carbon dioxide concentrations were evaluated individually using the following equation [15]

$$E = E_0 + k_1 C_e(t) + k_2 C_{ET}(t)$$

where E is the value of end-tidal carbon dioxide concentration at time t after the administration of oxycodone. E_0, k_1, $C_e(t)$, k_2 and $C_{ET}(t)$ are the respective values for baseline effect, the slope of the line relating effect to oxycodone concentration, the concentration of oxycodone at time t at the site of action, the slope of the line relating effect to end-tidal halothane concentration and the end-tidal concentration of halothane at time t. Because the same premedication and anaesthetic technique was used throughout the study, it was assumed that the effects of flunitrazepam, thiopentone, pancuronium, glycopyrrolate and neostigmine on ventilation were similar in all patients. Because of technical problems with our central monitoring computer and because of manual assistance of ventilation in four patients, complete continuous ventilatory and haemodynamic measurements were available only for 12 patients. Thus, the pharmacokinetic parameters could be calculated for all 18 patients but a pharmacokinetic-dynamic model could be constructed for 12 patients. The sigmoid E_{max} model was also applied to the relation between oxycodone and halothane concentrations and ventilation. However, owing to noise in the ventilatory measurements it was not possible to identify the parameters of this model.

$C_e(t)$ was estimated by two methods. First, assuming no equilibration delay between drug in plasma and that at the site of action (C=C_e). Secondly, by accounting for the possibility of a delay between the time-curves of plasma oxycodone concentration and effect using a pharmacokinetic-pharmacodynamic link model [16]. There was no provision for a possible equilibration delay between end-tidal concentration of halothane and its concentration at the effect site. Iterative reweighted least squares with reciprocal squared prediction weighting was used [10]. The 'best fit' was determined as described for the pharmacokinetic modelling. All results are given as mean ± s.d. unless stated otherwise.

Results

Pharmacokinetics

Plasma oxycodone concentrations are shown in Figure 1. Concentrations fell below the detection limit at 416 ± 94 min (range 240-600 min). Although plasma was planned to be sampled for 480 min only, one sample was taken at 600 min in the patient who was erroneously given 10 mg oxycodone instead of 2

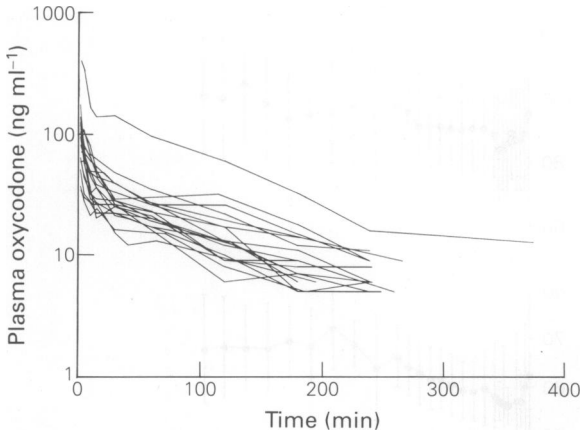

Figure 1 Plasma oxycodone concentrations in each of 18 children given oxycodone 0.1 mg kg^{-1} as an intravenous bolus.

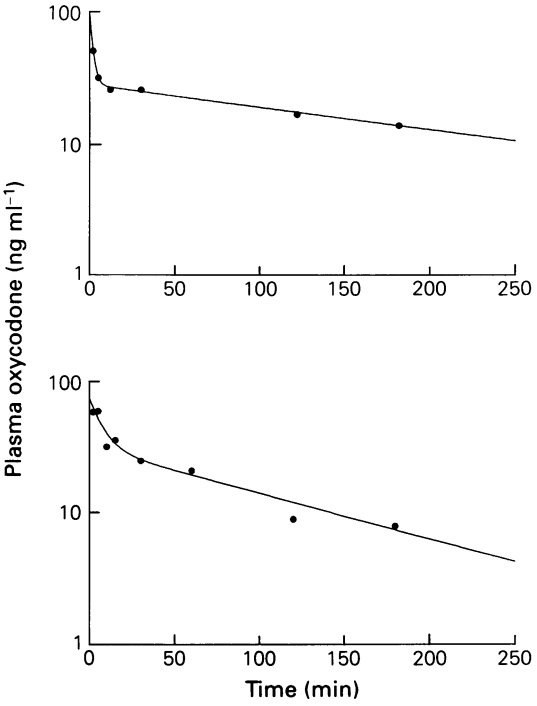

Figure 2 Plasma oxycodone concentrations after intravenous administration of 0.1 mg kg^{-1} of oxycodone hydrochloride to two patients. The upper panel shows data for patient 6, with the best fit of the pharmacokinetic model; the lower panel shows data for patient 10 with the worst fit (● observed data, — fitted function).

mg (patient number 9). There was only one patient in whom the detection limit was not reached. In this patient, for technical reasons, no samples were drawn after 182 min. A biexponential function gave the best fit to the data in all patients. The correlation coefficient between measured and predicted concentration ranged from 0.970 to 0.999. The best and worst fits are shown in Figure 2. Characteristics of the patients and the calculated pharmacokinetic parameters are summarized in Table 1. Values of $t_{1/2,,z}$, V_1, V_{ss} and CL were not correlated with age, weight or body surface area. Patient 9 was given 10 mg of oxycodone hydrochloride (0.5 mg kg^{-1}) in error. Her pharmacokinetic parameters did not differ from those of the other patients.

Pharmacodynamics

Mean values of ventilatory rate, $ETCO_2$, SpO_2, heart rate, mean arterial blood pressure and end-tidal halothane concentration after the administration of oxycodone hydrochloride are shown in Figure 3. The maximum of the mean $ETCO_2$ curve occurred at 8 min after administration of oxycodone as did the minimum of the mean ventilatory rate. The minimum of the mean SpO_2 occurred at 4 min. The mean of individual maximum $ETCO_2$ values was 8.2 ± 1.0% (range 6.7 to 10%). At 45 s after the administration of the 10 mg dose to patient 9 she stopped breathing and was ventilated manually with a face mask for 15

Table 1 Patient characteristics and pharmacokinetic parameters of oxycodone

Subject	*Age (years)*	*Weight (kg)*	$t_{1/2,l}$ *(min)*	$t_{1/2,z}$ *(min)*	V_1 *(l kg^{-1})*	V_{ss} *(l kg^{-1})*	*CL (ml min^{-1} kg^{-1})*
1	2.3	14.0	5.9	127	2.0	3.7	21.2
2	2.4	12.0	7.7	78	0.9	1.4	13.6
3	2.7	14.5	7.5	103	0.6	1.3	9.4
4	3.3	14.0	6.2	141	1.1	3.7	20.7
5	3.3	16.5	7.8	88	0.6	1.7	18.2
6	3.8	18.5	1.3	179	0.8	2.6	10.3
7	4.1	18.5	3.5	122	0.7	1.7	10.3
8	4.7	19.0	2.4	95	0.5	2.2	17.9
*9	6.1	20.0	2.9	101	0.6	2.2	16.7
10	6.2	21.5	5.3	87	1.1	2.1	18.5
11	6.5	22.0	1.4	73	0.3	1.3	13.5
12	6.6	24.0	2.7	88	0.9	2.4	19.9
13	6.8	25.0	3.9	114	0.4	1.3	8.5
14	6.9	31.5	4.2	94	0.5	2.1	18.0
15	7.0	19.0	2.0	95	0.3	1.8	15.4
16	7.2	22.0	5.3	107	0.6	1.9	13.6
17	7.6	26.0	1.2	99	0.2	1.2	9.3
18	9.8	41.0	2.7	115	1.9	2.9	17.6
Mean	5.4	21.1	4.1	106	0.8	2.1	15.2
s.d.	2.1	7.0	2.2	25	0.5	0.8	4.2

*Dose 10 mg.

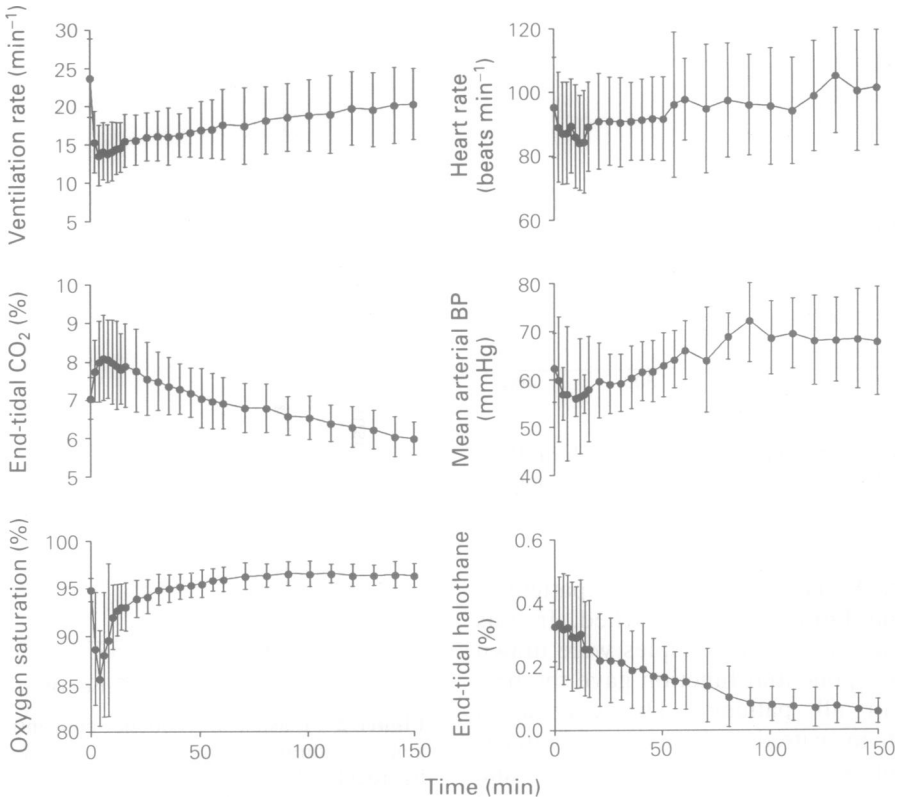

Figure 3 Mean ± s.d. ventilation rate, end-tidal carbon dioxide, oxygen and halothane concentrations, heart rate and mean arterial blood pressure in 12 children after intravenous administration of 0.1 mg kg^{-1} of oxycodone hydrochloride.

min. Additional oxygen was given for 43 min after drug administration. After the recovery of spontaneous ventilation, ventilatory rate remained 5-8 min^{-1} for 90 min. Later during the day the patient had an elevated body temperature up to 38.6-C and increased ventilatory rate (28-30 breaths min^{-1}) and heart rate (110–120 beats min^{-1}). She also had nausea and vomiting. Sixteen hours later the vital signs and body temperature were normal. In addition to this patient, three other patients had to be ventilated manually although they had been given the planned dose of oxycodone.

Heart rate and mean arterial blood pressure showed slight but clinically insignificant changes. Mean end-tidal halothane decreased from 0.32 to less than 0.1% in approximately 90 min. The duration of surgery was 52 ± 26 min. The mean time to wakening after the end of anaesthesia was 103 ± 27 min. During the day of operation 12 patients needed additional analgesia. The mean duration of analgesia was 172 ± 112 min (range 40–440 min). The theoretical concentration of oxycodone at the time of administering the rescue analgesic, based on the fitted function describing the pharmacokinetics of oxycodone in individual patients, was 12 ± 8 ng ml^{-1} (median 10 ng ml^{-1}, range 3–32 ng ml^{-1}). Altogether eight patients had nausea or vomiting and one patient did not urinate during the operation day.

The relationship between plasma oxycodone concentration and end-tidal halothane concentration and

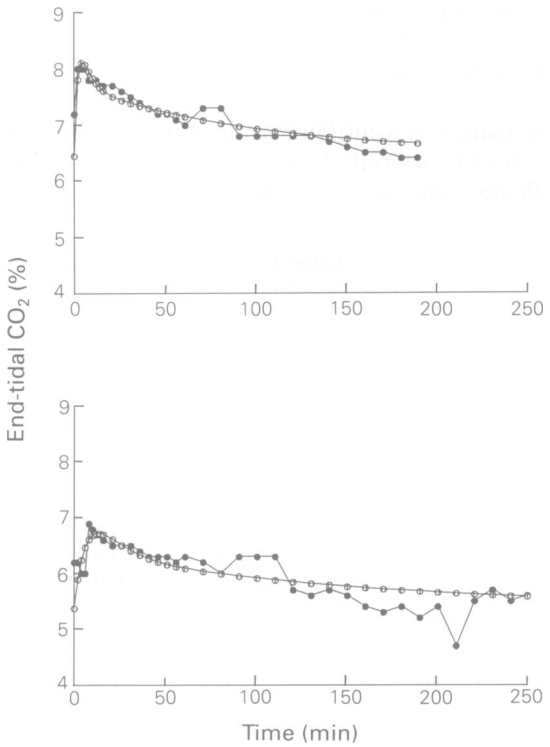

Figure 4 End-tidal carbon dioxide tension after intravenous administration of 0.1 mg kg^{-1} of oxycodone hydrochloride in two patients. The upper panel shows data for patient 13, with the best fit of the pharmacodynamic model; the lower panel shows data for patient 16, with the worst fit (● observed data, ○ fitted function).

Table 2 Pharmacodynamic parameters of a linear pharmacodynamic model describing the relation of plasma concentrations of oxycodone and end-tidal halothane to $ETCO_2$

Subject	*E* (%)	k_1 (% ng^{-1} ml)	k_2 (% ng^{-1} ml)	$t_{1/2}$ ($-k_{eo}$) (min)
2	5.2	0.054	3.5	2.6
3	4.8	0.025	2.2	2.0
5	5.3	0.029	7.6	6.5
6	6.0	0.016	0.2	1.6
7	5.7	0.046	4.6	10.4
8	5.4	0.039	3.1	8.9
10	5.4	0.037	2.6	2.3
11	6.3	0.019	2.1	4.8
12	5.1	0.065	3.0	7.0
13	6.9	0.032	2.0	6.1
16	5.2	0.027	1.9	8.1
17	3.8	0.058	23.8	9.1
Mean	5.4	0.037	4.7	5.8
s.d.	0.8	0.016	6.3	3.1

E, k_1 and k_2 are defined in the text, $t_{1/2}$ ($-k_{eo}$) refers to the half-life for equilibrium between plasma and effect site.

$ETCO_2$ was best described with a model which allowed a delay between the plasma concentration of oxycodone and the change in $ETCO_2$. The correlation coefficient between measured and predicted $ETCO_2$ ranged from 0.838 to 0.979. The best and worst fits of the pharmacodynamic data are shown on Figure 4. The calculated pharmacodynamic parameters are summarized in Table 2.

Discussion

The mean value of the $t_{1/2,z}$ of oxycodone was approximately 100 min, which is less than half that observed previously in adults who had been anaesthetized the day before administration of oxycodone [5]. However, a rapid fall of plasma oxycodone concentrations to below the detection limit might have resulted in underestimation of $t_{1/2,z}$. Compared with values of clearance in adults, those of children were almost 50% higher [5–7] and values of V_{ss} were 18% lower. Halothane anaesthesia decreases the metabolic clearance of drugs in liver [16]. Thus, the differences in oxycodone metabolism between children and adults may be even greater. In adults the clearance of pethidine was found to be less during anaesthesia than during the late postoperative period and in unanaesthetised subjects [17].

After the administration of oxycodone the ventilatory variables were characterized by remarkably rapid and steep changes. Major increases in $ETCO_2$ and decreases in ventilatory rate occurred in all patients. Mean $ETCO_2$ values appeared to be higher and mean ventilatory rates lower than observed earlier with morphine, buprenorphine, meperidine and methadone when given postoperatively to pediatric patients who had undergone eye surgery. Correspondingly, the mean SpO_2 values were lower and the minimum was reached earlier than with other opioids in children [18,19]. There are a limited number of studies on the relationship between plasma concentration and ventilatory effects of opioids in humans. To our knowledge, the relation of plasma oxycodone concentrations to ventilation has not been studied previously. According to the pharmacokinetic-dynamic model, the slope of the line relating change of $ETCO_2$ to oxycodone concentration was 0.045 ± 0.030% ng^{-1} ml. This indicates, for example, that the mean theoretical concentration of oxycodone at the site of action at the time of administering the rescue analgesic, 12 ng ml^{-1}, would increase $ETCO_2$ by 0.4% if halothane had been eliminated entirely from the body. This appears to be reasonable when oxycodone is given for patients not receiving oxycodone or other opioids chronically but less likely to be valid for patients being treated continuously with opioids because of development of tolerance.

In order to assess the effect of oxycodone on ventilation it would be ideal to administer the drug to healthy children who have not undergone surgery. However, this is impossible for ethical reasons. Therefore, oxycodone was given prophylactically after minor surgery, which usually requires administration of opioids. No opioids were administered for premedication or during anesthesia. In case of postoperative pain, intravenous diclofenac was chosen for the primary rescue analgesic because it does not affect ventilation [20]. Although the ventilatory measurements were perturbed by the fact that the children were emerging from anaesthesia, this setting allowed noninvasive measurements of ventilatory changes in a calm and cooperative child breathing room air. Noninvasive ventilatory measurements in children suffering from postoperative pain are impossible. The relatively high predrug mean $ETCO_2$ and ventilation rate values, 30 min after stopping halothane and extubation, were most likely due to residual halothane. However, the contribution of halothane to the changes in $ETCO_2$ following oxycodone was estimated using the pharmacokinetic-dynamic model. Although the integrated pharmacokinetic-dynamic model was able to demonstrate a linear relationship between between oxycodone and halothane concentrations and $ETCO_2$ it was difficult to separate the effects of oxycodone and halothane. However, each patient had at least one time point when plasma oxycodone concentration was zero and end-tidal halothane was not (the time before oxycodone was given). Furthermore, in most cases end-tidal halothane concentrations approached zero faster than plasma oxycodone concentrations. Therefore, we believe that our model can differentiate the effects of these two factors satisfactorily.

Duration of analgesia measured as the time to administration of rescue analgesia was 172 ± 112 min which is somewhat shorter than after 0.1 mg kg^{-1} of morphine and methadone and about the same as after 0.67 mg kg^{-1} of meperidine in comparable situations [18]. In adults the analgesic effect of oxycodone has

been shown to last somewhat longer than that of morphine. The discrepancy could be due to the fact that our study was not planned to investigate the analgesic efficacy of oxycodone. Pain after ophthalmic surgery is usually rather mild and it seldom requires several doses of opioids. The ventilatory depression observed after 0.1 mg kg^{-1} oxycodone in our patients appeared to be greater than following other opioids given in presumed equianalgesic doses to comparable patients [18,19].

In conclusion, oxycodone appears to be cleared faster in children than in adults. Since it appears to depress ventilation more than other opioids, it should be used with care in children emerging from anesthesia.

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