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BIOAVAILABILITY AND ABSORPTION RATE OF TRANSDERMAL FENTANYL

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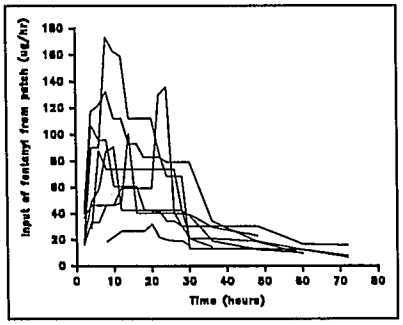
Introduction: This study was designed to determine the bioavailability and absorption rate of a new fentanyl transdermal delivery system (TDS). The patient's own disposition function and fentanyl clearance following intravenous fentanyl administration were used instead of population values to calculate the pharmacokinetic characteristics of the TDS.

Methods: After IRB approval and informed consent, we studied ten patients, ASA I-III, undergoing a variety of surgical procedures. Prior to induction of anesthesia, patients received an infusion of fentanyl at 150 µg/min for 5 min. On the first postoperative day (24 hrs after iv fentanyl administration), a TDS was placed on the anterior chest for 24 hrs. Blood samples were taken at predetermined times for 24 hrs after iv fentanyl and for 72 hrs after TDS placement. Plasma fentanyl levels were determined by RIA (limit = 0.2 ng/ml, ± 5% CV). Residual TDS fentanyl content in the patch was assayed to determine bioavailability. The area under the plasma concentration vs time curve for the iv part (AUC_{iv}) and TDS part (AUC_{TDS}) was calculated. Each subjects fentanyl clearance (Cl_{iv}) was calculated as dose iv/AUC_{iv}. The dose of fentanyl reaching the circulation from the TDS ($Fent_{TD}$) was calculated as the AUC_{TDS} * CL_{iv}. Bioavailability was calculated as $Fent_{TD}$/(initial TDS fentanyl - residual TDS fentanyl). Constrained numerical deconvolution was used to calculate the disposition function following the IV administration and the rate of absorption following TDS administration.

Results: The average clearance, TDS fentanyl delivered, initial - residual TDS fentanyl and bioavailability are shown in the table below. The figure to the right illustrates the rate of absorption from the TDS fentanyl patch, based on deconvolution. The average bioavailability was 47%.



Discussion: The TDS was intended to maintain plasma fentanyl concentration of 1.5 to 3.0 ug/ml for the period from 12 to 24 hrs. The anticipated peak rate of fentanyl delivery was approximately 100 µg/h. These goals were attained in the present study, but there was substantial variability. The apparent bioavailability of 47% is significantly less than previously reported for a different transdermal fentanyl device.[1] This illustrates the importance of carefully designed clinical studies to determine differences between devices that might otherwise be expected to behave identically.

References: 1. Anesthesiology 70:928-934, 1989

Patient	Cl_{iv} (liters/h)	$Fent_{TD}$ (mg)	Initial - Residual Fentanyl in Patch (mg)	Percent Bioavail.
1	49	2.6	3.5	76%
2	20	2.2	6.7	33%
3	63	1.3	4.5	30%
4	40	2.7	4.5	61%
5	55	1.0	6.8	14%
6	40	3.7	5.9	63%
7	30	2.8	4.9	57%
8	26	1.9	4.8	40%

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TITLE: INFLUENCE OF CROHN'S DISEASE ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF ALFENTANIL

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Patients with Crohn's disease have increased alfentanil (ALF) dose requirements during abdominal surgery.[1] We investigated whether this is due to altered pharmacokinetics or pharmacodynamics.

Methods: With Ethics committee approval and informed consent, 12 patients with (group 1) and 10 without (group 2) Crohn's disease, age 20-59 yr, ASA 1 or 2, undergoing abdominal surgery were studied. Premedication was with midazolam, 0.1 mg/kg IM. Anesthesia was induced with ALF, 0.1 mg/kg and thiopental 2-4 mg/kg, followed by ALF, 50 µg/kg/h. Succinylcholine, 1 mg/kg, was given, the trachea intubated and the lungs ventilated with 66% N_2O in O_2. If during surgery patients exhibited signs of inadequate anesthesia a bolus of ALF, 10 µg/kg, was given and the infusion rate increased by 25 µg/kg/h to a maximum of 200 µg/kg/h. Inadequate anesthesia was defined as an increase in systolic blood pressure and/or heart rate by >20% above preoperative value or other autonomic or somatic responses. If a patient did not respond during 15 min the ALF infusion rate was decreased by 25 µg/kg/h to a minimum of 25 µg/kg/h. ALF infusion was stopped 10 min before the end of surgery. Patients were extubated when ventilation was adequate without stimulation. If, 10 min after surgery ventilation was inadequate naloxone was given. Arterial blood samples were taken 2,7 and 15 min after starting ALF infusion and every 30 min thereafter. A sample was also obtained before any change in infusion rate and 2,7 and 15 min after an ALF bolus. After stopping the infusion, samples were collected for 6h. A sample was also taken at extubation. Plasma concentrations were determined by GLC. Pharmacokinetic data were derived using non compartmental techniques. Concentration-effect (response or no response) data were fitted by logistic regression. The Mann-Whitney U-test was used for comparisons. $P<0.05$ was considered significant.

Results: ALF dose requirements were higher in group 1, as were plasma concentrations at extubation (Cp ext) in patients who did not need naloxone and Cp50 (plasma concentration for which the probability of no response during surgery is 50%). Pharmacokinetics were similar in both groups (table).

Discussion: This study confirmed the earlier reported increase in ALF dose requirements in patients with Crohn's disease and demonstrated that this is due to altered pharmacodynamics.

Reference: Anaesthesia 44: 209-212, 1989.

Table. Dose Requirements (DR), Pharmacodynamic and Pharmacokinetic Data.

	Group 1	Group 2
DR (µg/kg/min)	2.37 (1.04-4.44)	1.10 (0.65-2.87)*
Cp50 (ng/ml)	329 (108-615)	201 (59-389)*
Cp ext (ng/ml)+	236 (101-797)	133 (43-210)*
$t_{\frac{1}{2},z}$ (min)	74 (43-144)	82 (43-132)
CL (ml/kg/min)	6.1 (2.7-8.4)	5.2 (2.5-14.0)
Vss (l/kg)	0.70 (0.41-0.97)	0.58 (0.31-1.20)

+patients requiring naloxone excluded
Group 1 vs group 2: *P<0.02