PHARMACOKINETICS OF FENTANYL AS A POSSIBLE EXPLANATION FOR RECURRENCE OF RESPIRATORY DEPRESSION

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SUMMARY

The pharmacokinetics of fentanyl are complicated by an additional increase in plasma concentration during the elimination phase of the drug. We have confirmed that fentanyl is excreted in the gastric juice and reabsorbed from the alkaline medium of the small intestine. In addition, the stomach wall in rats has an important storage capacity for fentanyl. A maximum of about 20% of the dose was found in the stomach wall after i.v. injection. In man the resected part of the stomach contained 16% of the dose, 10 min after injection. These observations could be important in explaining the occurrence of respiratory depression in the period after operation.

Becker and others (1976) reported biphasic respiratory depression after fentanyl was used to supplement nitrous oxide anaesthesia. Adams and Pybus (1978) reported three patients who suffered severe respiratory depression after apparent recovery from a general anaesthetic which included fentanyl; this was treated successfully with naloxone.

We have investigated the disposition of fentanyl in patients who received fentanyl during the course of clinical anaesthesia.

METHODS

Fentanyl was obtained as the citrate salt in 10-ml vials as available commercially. Doses and concentrations given refer to the free base. Concentrations of fentanyl in biological material were determined by radioimmunoassay (Michiels, Hendriks, and Heykants, 1977). The coefficient of variation was ±5% for a concentration of 1 ng ml⁻¹ (0.97 ± 0.05 ng ml⁻¹) and ±10.2% for a 5-ng ml⁻¹ sample.

Seven patients undergoing abdominal hysterectomy gave informed consent to the study. Premedication comprised promethazine 50 mg and atropine 0.5 mg, i.m. 1 h before operation. Anaesthesia was induced with methohexitone 1 mg kg⁻¹. Suxamethonium 1.5 mg kg⁻¹ was given to facilitate tracheal intubation. Anaesthesia was maintained with 1.0% halothane, and 60% nitrous oxide in oxygen. Myoneural blockade was maintained with pancuronium bromide (total dose 6 mg). The lungs were ventilated artificially with a semi-closed system (Spiromat 650, Dräger). A bolus dose of fentanyl 0.5 mg was given into a forearm vein immediately following tracheal intubation. Blood was sampled through a plastic cannula at 2, 5, 7, 10, 15, 20, 30, 45, 60, 90 and 120 min after injection. Gastric juice was aspirated through a gastric tube after filling the stomach with 200 ml of physiological saline at 37 °C.

In five healthy male volunteers, age range 24–32 yr, an aqueous solution of 0.3 mg of fentanyl base was administered orally after an overnight fast. Venous blood was sampled from a forearm vein at 15, 30, 45, 60, 75, 90, 120, 180 and 240 min after ingestion.

Three dogs (average weight 15 kg) were anaesthetized with pentobarbitone 15 mg kg⁻¹. After laparotomy the pylorus was ligated and oesophageal reflux was prevented by a Sengstaken–Blakemore probe. At 5, 10, 20, 30, 40, 50, 60 and 90 min after i.v. injection of fentanyl 0.25 mg the stomach was flushed with acidified (pH 3.0) physiological saline.

For the determination of fentanyl concentration in brain, lungs and stomach wall, 20 female Sprague–Dawley rats received fentanyl 5 μg per 100 g body weight into the tail vein. After a short period of intermittent compression of the chest wall, animals in groups of five were decapitated at 10, 20, 40 and 80 min. The organs were removed and homogenized in 2 × 5 ml of absolute methanol. After 12 h at 4 °C the protein was spun down by centrifugation. The methanolic supernatant was diluted 1:5 with phosphate buffer 0.05 mol litre⁻¹ (pH 7.4).

Recovery from organ homogenates was determined after addition of 50 000 counts ³H-fentanyl (= 1 ng) to the brain, lungs and stomach of five rats. After
homogenization, 75% of the radioactivity was recovered in the supernatant of lungs and stomach and 85% in brain. Our results are not corrected for this recovery rate.

This same procedure was carried out for tissue samples of the resected part of human stomach in six patients who received fentanyl base 0.5 mg during general anaesthesia for Billroth II gastrectomy. Regression analysis for the individual time-log concentration pairs was by the method of least squares.

RESULTS

Patient study

Large initial plasma fentanyl concentrations were observed following a bolus dose of 0.5 mg (50-100 ng ml\(^{-1}\)). In many patients a secondary increase in plasma concentration was seen, but the time course of the changes was variable. Peak concentrations occurred 20-90 min after injection (figs 1 and 2).

Furthermore, the area under the curve of these secondary peaks differed considerably.

Following oral administration of fentanyl 0.3 mg in aqueous solution a peak plasma concentration occurred at about 90 min (fig. 3). The area under the curve (corrected for the dose administered) was about one-third of that following i.v. injection (767 v. 2417 ng ml\(^{-1}\) min) indicating reduced enteric absorption after ingestion.

The concentration of fentanyl in gastric juice was determined in seven patients following a bolus injection of fentanyl. A typical example is demonstrated in figure 4. During the rapid reduction in plasma concentrations, fentanyl up to 400 ng min\(^{-1}\)
was detected in the gastric juice. The total amount secreted in gastric juice was estimated as 3–4\% of the injected dose. However, a loss of gastric juice during the collection periods was suspected because of the inflection in the plasma concentration curve.

In patients undergoing surgery for gastrectomy it was not possible to set a time interval between injection of fentanyl and isolation of the stomach from the circulation. The time intervals varied from 34 to 105 min. Assuming linear elimination kinetics for the stomach wall, it is possible to calculate by regression analysis the amount of fentanyl within this organ. A regression coefficient (r) of 0.91 revealed a good fit for the calculated curve. Using the equation for this regression line (fig. 5), we calculated that about 16\% of the dose was located in the stomach 10 min after injection.

\[ y = ax + b \]

\[ r = 0.91 \]

**Animal study**

After bolus i.v. injection of fentanyl 0.25 mg in dogs the decay of plasma concentrations was that of a two-compartment open model. There was no secondary increase during the 2 h of the experiment. When the gastric outlet was closed the cumulative amount of fentanyl in gastric juice was approximately 10\% of the dose when extrapolated to infinity (fig. 6).

The concentrations of fentanyl in the rat organ homogenates of brain and lungs decreased from the first determination at 10 min. The concentration in the stomach wall reached a maximum at 20 min corresponding to approximately 20\% of the dose.

Even at the latest point determined (80 min), 10\% of the dose still remained within the stomach (fig. 7).

**DISCUSSION**

In most of our patients, plasma concentrations of fentanyl could be analysed according to a two-compartment open model (Hess, Stiebler and Herz, 1972) described for tritiated fentanyl. In some patients, however, variations could be seen (figs 1 and 2) and when we shortened the interval between blood collections, nearly all the patients investigated showed a secondary increase in plasma concentration of fentanyl.
A possible explanation for this phenomenon is an entero-systemic recirculation as described by Schanker and others (1958) for basic drugs in general, by Trudnowski and Gessner (1975) for pethidine and by Lynn and others (1976) for methadone. Therefore, we studied gastric secretion and absorption of fentanyl from the gut in man.

The most likely moment for the appearance of fentanyl in gastric juice would be immediately following injection, when the greatest concentration gradient occurs between blood and stomach wall and gastric juice. Our studies showed an increasing concentration of fentanyl in the gastric juice of man up to 30 min after i.v. injection. The gastric excretion rates decreased thereafter approximately in parallel with the serum concentrations.

Calculation of the amount of fentanyl secreted into gastric juice was not exact because of the difficulty in ensuring complete collection of juice. In the dog, with a ligated pylorus, as much as 7% of the i.v. dose could be collected in gastric juice. Extrapolation to infinity revealed a cumulative amount of about 10% of the dose. However, this may be less than that observed in man because the plasma concentrations in the dog following the injection of the drug even in large doses (0.02 v. 0.01 mg kg"^-1") were not as great as in man.

The stomach wall both secretes and stores fentanyl. About 20% of the dose was located in the stomach wall at 20 min after injection, a value twice that in lung and brain. In man, storage was also demonstrated by extrapolation of data from random samples of human stomach wall in six patients. We calculated that about 16% of the dose was retained in the stomach wall.

We demonstrated that fentanyl was secreted into gastric juice after i.v. injection. In man the measurement of plasma concentrations following an oral dose of fentanyl revealed absorption from the gut, but with an availability of only 33%. The total amount absorbed (amount secreted reduced by the bio-availability factor) was calculated to be about 5% of the injected dose.

The time of onset and the extent of this mechanism may limit the pharmacological effects in patients. This additional amount of fentanyl may be negligible when compared with the total dose injected. However, at the time of appearance of the reabsorbed fentanyl, at about 30–60 min, more than 75% of the injected dose is located in the peripheral compartment (Hengstmann, Stoeckel and Schüttler, 1978). The pharmacokinetic properties imply a rapid transfer of drug into the peripheral compartment of the two-compartment open model. This amount, together with the amount entering the compartment after reabsorption, may be sufficient to cause acute respiratory insufficiency or reduced sensitivity of the chemoreceptors to carbon dioxide. This may occur even at 4 h after drug injection (Becker et al., 1976) when only about 20% of the dose is stored in the peripheral tissues (Stoeckel et al., 1979). The significance of this concept can only be judged from simultaneous measurement of plasma concentrations and testing for possible respiratory depression following fentanyl analgesia.

ACKNOWLEDGEMENTS

We are grateful to Drs Michiels and Heykants, Janssen Pharmaceutica, Research Laboratoria, Beerse/Belgium, for the gift of H-fentanyl and fentanyl antibodies.

This work was supported by a grant from Ministerium für Wissenschaft und Forschung, NRW, Germany (06/0604/68511).

J. H. H. was supported by Deutsche Forschungsgemeinschaft (He 791).

REFERENCES


PHARMACOKINETICS OF FENTANYL

PHARMACOCINETIQUE DU FENTANYL
EN TANT QU’EXPLICATION POSSIBLE
DE LA REPETITION DE LA DEPRESSION
RESPIRATOIRE

RESUME
La pharmacocinétique du fentanyl est compliquée par
l’augmentation supplémentaire des concentrations dans
le plasma qui se produisent pendant la phase éliminatoire
de ce médicament. Nous avons confirmé que le fentanyl
s’éliminait dans le suc gastrique et était réabsorbé par la
substance alcaline de l’intestin grêle. De plus, la paroi
stomacale des rats a une capacité importante de stockage
du fentanyl. On a trouvé un maximum de 20% environ de
la dose dans la paroi stomacale après injection intraveineuse.
Chez l’homme, la résection d’une partie de l’estomac a fait
ressortir qu’il contenait 16% de la dose, 10 mn après
l’injection. Ces observations pourraient être importantes
pour expliquer l’apparition de dépression respiratoire au
 cours de la période qui suit l’intervention chirurgicale.

DIE PHARMAKOKINETIK VON PENTANYL
ALS MÖGLICHE ERKLÄRUNG FÜR DAS
WIEDERAUFTRETN VON RESPIRATORISCHER
DEPRESSION

ZUSAMMENFASSUNG
Das lineare pharmakokinetische Verhalten von Fentanyl
wird durch ein Wiederausteigen der Blutspiegel während
der Eliminationsphase dieses Pharmakons gestört. Wir
stellten fast, dass das basische Fentanyl in den Magen
sezerniert wird und vom alkalischen Dünndarmmilieu
reabsorbiert wird. Darüberhinaus besitzt auch die Magen-
wand eine erhebliche Speicherkapazität für das Pharmakon
Fentanyl. Bei Ratten fanden wir 20% der intravenösen
applizierten Dosis in der Magenwand. Im resezierten
Magenanteil von Patienten nach Billroth II Magenresektion
fanden wir 16% der applizierten Fentanyldosis 10 Min
nach Injektion. Diese Beobachtungen bieten sich als
mögliche Erklärung für das Wiederauftreten der Atem-
depression nach Ende der klinischen Fentanylästhesie an.

FARMACOCINETICA DEL FENTANIL COMO
POSSIBLE EXPLICACION DE LA RECURRENcia
DE DEPRESION RESPIRATORIA

SUMARIO
La farmacocinética del fentanilo se complica por un
aumento adicional en la concentración plasmática durante
la fase de eliminación de la substancia. Confirmamos que el
fentanilo se excreta en los jugos gástricos y se reabsorbe a
partir del medio alcalino del intestino delgado. Además, la
pared estomacal en los ratones posee una importante
capacidad de almacenamiento de fentanilo. Se encontró un
máximo del 20% aproximadamente de la dosis en su pared
estomacal después de una inyección i.v. En el hombre, la
parte resecada del estómago contenía un 16% de la
dosis, 10 min después de la inyección. Estas observaciones
podrían revestir importancia para explicar la ocurrencia de
despresiones respiratorias en el periodo post-operatorio.