EFFECT OF ANHEPATIC PHASE OF SURGERY USING VENO-VENOUS BYPASS TECHNIQUE ON PLASMA FENTANYL CONCENTRATION REPORT OF TWO CASES

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SUMMARY

We administered fentanyl continuously and measured its concentration in plasma in two patients undergoing surgery which produced an anhepatic phase using the veno-venous bypass technique; one patient had extracorporal liver resection and the other had venoplasty of the inferior vena cava and the right hepatic vein. The plasma fentanyl concentration increased during the anhepatic phase and decreased in the post-anhepatic phase in both cases. Though fentanyl has a wide safety margin, attention must be paid to such drug characteristics in the management of anaesthesia during the anhepatic phase.

KEY WORDS

fentanyl, continuous infusion, intravenous, anhepatic phase, veno-venous bypass

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INTRODUCTION

Operations, such as liver transplantation and extracorporal liver resection, that produce an anhepatic phase by interrupting the liver blood flow under veno-venous bypass have been increasing /1-3/. However, little is known about the kinetics of drugs such as anaesthetics in the anhepatic phase, i.e., the absence of the liver that is the main organ for drug metabolism.

Fentanyl has become a major anaesthetic agent for patients with unstable cardiovascular systems, including those undergoing liver transplantation. As fentanyl is eliminated and metabolized mainly in the liver, it is speculated that plasma fentanyl concentration would increase during the anhepatic phase, when fentanyl is infused continously. The possible increase of fentanyl concentration during the anhepatic phase is of great concern.

We evaluated the time course of plasma fentanyl concentration in two patients undergoing liver surgery which produced an anhepatic phase.

CASE REPORT

Case 1 was a 48 year-old man (height, 172 cm; weight, 64 kg) who underwent extracorporal liver resection after a diagnosis of bile duct tumour. Case 2 was a 31 year-old man (height, 157 cm; weight, 56 kg) with Budd-Chiari syndrome who underwent veneplasty of the inferior vena cava and the right hepatic vein. Preoperative laboratory studies revealed an increase in serum transaminases (SGOT 96 units. l^{-1}; SGPT 224 units.l^{-1}) and indocyanine green (ICG) retention at 15 min (29%) in case 1. In case 2 transaminases were not increased (SGOT, 32 units.l^{-1}, GPT, 20 units.l^{-1}) but ICG retention at 15 min was increased (17-26%).

Anaesthetic and operational course

Both patients were pre-medicated with 0.5 mg of atropine sulphate and 50 mg of hydroxyzine hydrochloride 30 minutes before induction of anaesthesia. After the i.v. line was inserted, a continuous epidural catheter with a 17-gauge Tuohy needle was inserted in the Th7-8 interlaminar space.

Anaesthesia was induced with 2.3 $mg.kg^{-1}$ of thiamiral immediately followed by 4.6 $\mu g.kg^{-1}$ of fentanyl, 0.13 $mg.kg^{-1}$ of vecuronium and 0.05 $mg.kg^{-1}$ of midazolam. General anaesthesia was maintained with 70% nitrous oxide in oxygen supplemented with isoflurane (0.25-0.5%). Bolus adminstration of 1.5% mepivacaine (2.3 $mg.kg^{-1}$, once an hour) into the epidural catheter was also used to maintain the anaesthesia. After the operative procedure was determined, the epidural infusion was terminated and a bolus of fentanyl (7.3 $ng.kg^{-1}$ in case 1 and 9.4 $ng.kg^{-1}$ in case 2) was given, followed by continuous infusion of fentanyl (3.1 $\mu g.kg^{-1}.hr^{-1}$ in both cases) with an infusion pump (Terumo STC-525). A supplementary dose of isoflurane (0-1.0%) was administrated as necessary.

In case 1, the anhepatic phase began 5 hours and 30 minutes after the induction of anaesthesia and lasted 4 hours 50 minutes. In case 2, the anhepatic phase began 9 hours and 55 minutes after the induction of anaesthesia and lasted for 3 hours and 45 minutes. During the anhepatic phase, veno-venous bypass (as described by Griffith *et al.* /4/) was performed. The femoral and portal vein cannulae were joined with a Y-connector leading to a centripetal force pump (Bio-Medicus model 510 console) and return flow was to the axillary vein. Flow was maintained at 1,000-1,200 $ml.min^{-1}$ in case 1 and 800-1,300 $ml.min^{-1}$ in case 2.

The operation required 15 hours in case 1 and 16 hours in case 2. Anaesthetic time was 17 hours in case 1 and 19 hours and 30 minutes in case 2. Total bleeding volume was 3,000 ml in case 1 and 15,000 ml in case 2.

Measurement

Blood samples were collected from an arterial catheter in the radial artery into heparinized glass tubes and immediately placed on ice. These samples were subsequently centrifuged, and the plasma was stored at -70°C until measurement. The plasma fentanyl concentrations were measured by the method of Lin *et al.* /15/. The gas chromatograph-mass spectrometer used was a Hewlett Packard Model 5988 equipped with a capillary column (J&W DB-1; I.D. 0.25 mm; length, 20 m).

RESULTS

Figure 1 shows the time course of plasma fentanyl concentration during the operation in case 1. Before bolus administration the plasma fentanyl was undetectable (detection limit: 0.5 $ng.ml^{-1}$). After bolus administration the plasma fentanyl concentration during the pre-anhepatic phase ranged from 8.4 $ng.ml^{-1}$ to 16.0 $\mu g.ml^{-1}$ and mean concentration was 11.4 $ng.ml^{-1}$. During the anhepatic phase plasma fentanyl concentration increased about twofold (range, 15.3 - 30.3 $ng.ml^{-1}$; mean, 22.3 $ng.ml^{-1}$) compared with the pre-anhepatic phase. During the post-anhepatic phase, plasma fentanyl concentration decreased to almost one-third compared with the anhepatic phase (range, 3.1 - 6.2 $ng.ml^{-1}$; mean, 6.9 $ng.ml^{-1}$).

Figure 2 shows the time couse of plasma fentanyl concentration in case 2. Before the start of the continuous infusion, the plasma fentanyl concentration was below the detectable limit. The plasma fentanyl concentration was 2.2 - 4.6 $ng.ml^{-1}$ (mean, 3.7 $ng.ml^{-1}$) in the pre-anhepatic phase but increased about 1.4 times (range, 3.8 - 4.6 $ng.ml^{-1}$; mean, 5.3 $ng.ml^{-1}$) in the anhepatic phase. It decreased during the post-anhepatic phase to two-thirds of the anhepatic concentration (range, 3.1 - 4.0 $ng.ml^{-1}$; mean, 3.5 $ng.ml^{-1}$).

DISCUSSION

Fentanyl is metabolized and eliminated mainly in the liver, and most administered fentanyl is ultimately excreted in the form of fentanyl metabolites in urine /6, 7/. Kang *et al.* /8/ reported that the rate of fentanyl biotransformation was decreased in patients with liver disease. Hug *et al.* /9/ demonstrated that the elimination half-life of fentanyl is remarkably increased in anhepatic dogs. The effect of impaired or absent liver function on the metabolism and elimination of fentanyl in humans is unknown.

The factors that could have affected the blood concentration of fentanyl in these two patients were the multiplicity of drugs used, changes in the metabolic rat due to hypothermia, changes of blood flow in excretory organs, changes of the circulating blood volume and of the blood distribution volume.

The increase of fentanyl plasma concentrations in these two patients could well be due to both decreased drug distribution and the absence of hepatic elimination. We cannot separate these two mech-

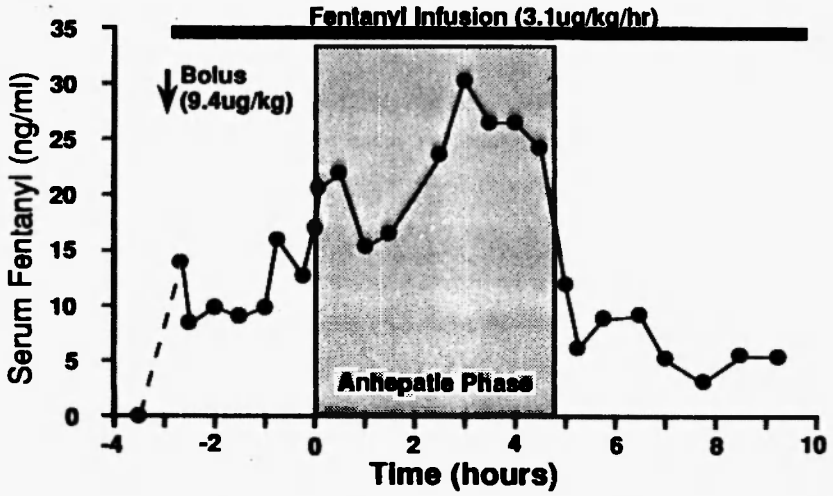

Fig. 1: Changes of plasma fentanyl concentration during the operation in case 1. Time zero is the start of the anhepatic phase. The shaded area represents the anhepatic phase.

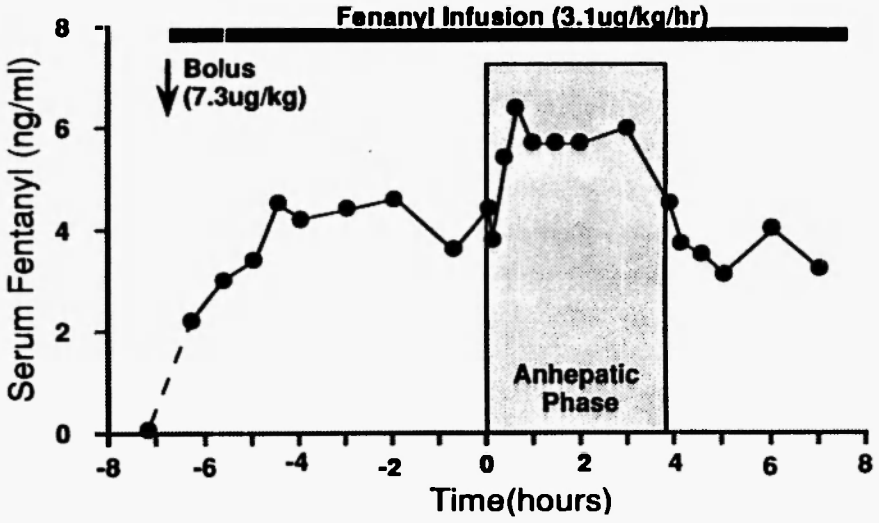

Fig. 2: Changes of plasma fentanyl concentrations during the operation in case 2. Time zero is the start of the anhepatic phase. The shaded area represents the anhepatic phase.

anisms in our data. Thus, it is not possible to know whether the increased fentanyl plasma concentrations observed were due to the decreased rate of drug distribution to tissues from the intra-abdominal manipulation or to the lack of hepatic metabolism.

In conclusion, fentanyl has a wide safety margin, but attention should be paid to such drug characteristics in the management of anaesthesia during the anhepatic phase. Further studies are needed to assess changes in blood concentrations of various drugs during the anhepatic phase.

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