Pharmacokinetics of controlled release morphine (MST) in patients with liver carcinoma

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Background. There are no studies reported on the pharmacokinetics of controlled release morphine (MST) in patients with hepatocellular carcinoma, the fifth most common cancer in the world.

Methods. We have studied the pharmacokinetic profile of MST (30 mg) in 15 patients with liver carcinoma (eight with primary carcinoma on top of chronic hepatitis C, and seven with secondary metastatic liver malignancy as a result of other primary) compared with our previously published data for 10 healthy controls. Plasma morphine concentrations were measured in venous blood samples at intervals up to 12 h by high-pressure liquid chromatography. Total body clearance (Cl) and systemic bioavailability were estimated using a compartmental method.

Results. Morphine bioavailability showed a substantial increase in patients with primary liver and secondary metastatic carcinoma than that of controls (64.8, 62.1, and 16.8%, respectively). The area under the serum concentration–time curve increased 4-fold in primary carcinoma (416 [SEM 25] μg h⁻¹ litre⁻¹) and 3-fold (303 [21] μg h⁻¹ litre⁻¹) in metastatic liver patients compared with healthy control (92.5 [3] μg h⁻¹ litre⁻¹). No significant difference was found in Tₘax between the two malignant groups but Cₘax was significantly greater in primary liver carcinoma patients. Impaired morphine elimination was noted in primary carcinoma only (t₁/₂ 5.99 [0.39] h).

Conclusion. Careful administration of morphine is recommended in patients with liver cancer.

Keywords: analgesics opioid, morphine; drug deliver, oral; liver, disease; pharmacokinetics, morphine; pharmacology, morphine

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difference in the time of which blood morphine concentrations were more than/equal to 75\% of $C_{\text{max}}$.

The inclusion criteria were adult patients with documented (pathological and radiological) evidence of liver cancer requiring the prescription of oral morphine to control moderate to severe pain. Exclusion criteria were, significant abnormalities in hepatic, renal, hematological, or pulmonary function and any gastrointestinal pathology or surgery, which could influence the absorption of morphine. Other exclusion criteria included patients undergoing chemotherapy or radiotherapy, intractable vomiting or patients who could not swallow a tablet and patients with a history of drug seeking behaviour or any other medication that can alter hepatic blood flow/enzyme activity.

**Study protocol**

The study protocol was reviewed and approved by The Ethics Committee at Assiut Faculty of Medicine. All patients gave their acceptance to participate in this study and signed informed consent.

The protocol included two groups of cancer liver patients. Group I: primary liver cancer associated with cirrhosis (eight patients). Their mean age was 59.3 (50–70) yr; mean weight 66.8 (SD 9.9) kg. All had carcinoma on top of chronic hepatitis C. All had been investigated thoroughly including hepato-renal function, serum albumin, total plasma protein, transaminases and bilirubin, ultrasound, and liver biopsy. Computerized topographic (CT) findings demonstrated the presence of focal lesions in the liver as well as cirrhosis. Group II: secondary metastatic liver malignancy (seven patients). Their mean age was 52 (40–60) yr; mean weight 65 (SD 7) kg. Their inclusion was based upon diagnosis of the primary plus ultrasonographic picture of an enlarged liver with metastasis with no evidence of cirrhosis. CT findings demonstrated enlarged liver with multiple focal lesions. Serum albumin, serum bilirubin, and total protein concentrations were all within the normal range. Both groups were opioid naïve.

The study protocol included also 10 healthy control subjects previously given 30 mg (MST) to serve as our study control. They all had normal renal and liver function with negative tests for hepatitis.\(^6\) Administration of morphine was started at 10:00 in all patients. A cannula was inserted into an antecubital vein under local anaesthesia to facilitate sampling of venous blood. Blood was obtained every 30 min for the first 3 h, followed by every hour for the next 3 h, and then every 2 h up to 12 h.

Plasma concentrations of morphine were measured by high-pressure liquid chromatography using a fluorescence response. The limit of quantification was 2 ng ml\(^{-1}\), with a coefficient of variation of less than 3\%. Morphine concentrations at different times after oral MST 30 mg were fitted to a two-compartment model, where, the total body clearance (Cl) and bioavailability ($F$) were calculated. The differential equations of the proposed model were analysed using the MULTI (Rung computer) program.\(^7\) The mean residence time MRT was calculated using the following equation:

$$\text{MRT} = \frac{k_{12} + k_{21}}{k_{10} \cdot k_{21}} + \frac{1}{k_a}$$

where $k_a$ is the absorption rate constant. $k_{12}$, $k_{21}$ are the intercompartmental rate constants. $k_{10}$ is the elimination rate constant.

The other parameters including maximum concentration in the blood concentration curve ($C_{\text{max}}$) and the time to reach that concentration ($T_{\text{max}}$) were obtained graphically. The area under the serum concentration–time curve (AUC) was determined using the the trapezoidal rule. The half-life of the elimination phase ($T_{1/2}$) was calculated using the slope of the elimination phase.

$$T_{1/2B} = 0.693/\beta.$$

The total body clearance was calculated using the following equation:

$$\text{Cl} = \frac{\text{Dose} \cdot F}{\text{AUC}}$$

**Data analysis**

All values shown are mean (SEM) of number of observations. All mean values between groups were analysed by one-way analysis of variance. Differences between groups were considered significant when $P<0.05$.

Pharmacodynamic efficacy variables of oral MST were assessed using verbal rating scale; 0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain. The level of sedation was assessed by using a similar scale; 0=alert and active, 1=awake and calm, 2=drowsy but respond to verbal and tactile stimuli, 3=asleep. All data concerning pain and sedation were collected by a blinded physician observer.

Patients were kept in the ICU with continuous monitoring of ECG, arterial blood pressure, pulse oximetry, and ventilatory frequency for 24 h post-drug administration.

**Results**

**Pharmacokinetics**

Plasma concentrations of morphine over the 12-h study are shown in Figure 1. Morphine was present in the blood within the first 30 min of the study in both controls and patients. In controls, the curve showed a decreasing trend after 5 h of sustained plasma concentration with no secondary peak. A higher peak was reached in patients with sustained concentration almost above that in controls over the study period.

The decay in plasma morphine concentration fitted best to biexponential function in all patients. Kinetic data were derived from the morphine concentration–time curve (Fig. 2).
The individual pharmacokinetic parameters for the control, primary, and secondary cancer liver patients after oral administration of MST 30 mg tablets are shown in Table 1. Table 2 shows the liver function test of the patients.  

C<sub>max</sub> was significantly higher in the primary cancer group (C<sub>max</sub> 52.7 [1.93] ng ml<sup>−1</sup>) and in the secondary cancer group (C<sub>max</sub> 39.44 [2.80] ng ml<sup>−1</sup>) compared with control (C<sub>max</sub> 12.81 [0.47] ng ml<sup>−1</sup>) (P<0.05). But still there were also significant differences between the primary and secondary cancer groups.

T<sub>max</sub> was similar in the primary cancer and secondary cancer groups (180 [0.00] min) but there was a significant difference between the two cancer groups and the control group (142.50 [4.9] min).

Systemic bioavailability (F%) was significantly higher (4-fold) in the primary group (F 64.8%) than in the control group (F 16.8%) and (3-fold) significantly higher in secondary group (F 62.1%) than the controls (P<0.05).

AUC in the patients was significantly increased compared with controls. There was also a significant difference between primary and secondary metastatic groups of patients (P<0.05).

There was no significant difference in MRT between the control (7.03 [0.61] h), primary (8.04 [0.45] h) and the secondary groups (7.03 [0.61] h). T<sub>1/2</sub> was significantly higher in the primary group (5.99 [0.39] h) compared with the control (4.01 [0.15] h) and the secondary group (4.61 [0.39] h). The total body clearance was higher in the secondary group (1.01 litre h<sup>−1</sup> kg<sup>−1</sup>) compared with the control group (0.73 litre h<sup>−1</sup> kg<sup>−1</sup>) and in the primary group (0.70 litre h<sup>−1</sup> kg<sup>−1</sup>), all changes were statistically insignificant.

Pharmacodynamics

After oral morphine administration all the studied patients expressed patient satisfaction and complete pain relief. The side-effects were more pronounced in the primary liver cancer group: two cases of respiratory depression occurred in this group. In both cases it was noted by a gradual decline in oxygen saturation measured by pulse oxymeter, decrease in the ventilatory frequency, and sedation 3 h after morphine administration. They responded to nalbuphine administration and mechanical ventilation was not needed in any of them. Estimated serum morphine levels at that time were 52 and 56 ng ml<sup>−1</sup>, respectively.

In the secondary cancer group the side-effects were sedation (six cases, sedated but arousable) and nausea (one case with cancer pylorus).

Discussion

We have determined the pharmacokinetics of oral morphine (MST 30 mg) in patients with liver carcinoma associated with cirrhosis or secondary to primary carcinoma. Derived kinetic variables in control healthy volunteers have been published and fitted closely to other reported data.6

Patients with liver cancer showed a 3–4-fold increase in the peak concentration of morphine presumably as a result of the reduction in first pass metabolism secondary to a reduction in liver cell mass; this led to an increase in total systemic
bioavailability of morphine. Approximately 70% of the dose entered the systemic circulation in patients with liver cancer compared with 20% in healthy control. This is reflected in an increase in the AUC.

Systemic clearance was maintained in liver cancer patients with a prolonged elimination half-life in patients with primary liver carcinoma as a result of cirrhosis. Early studies produced conflicting evidence on the effect of the liver cancer on hepatic drug metabolism; limited information is available on hepatic drug metabolism in primary and secondary liver cancer. Based on the intact hepatocyte theory Kawasak and co-workers showed that in a group of six patients with liver cancer (three primary and three metastatic) phenazone clearance was unchanged. Clearance of antipyrine was also reported in an increase in the AUC.

Clearance factors of antipyrine in a group of six patients with liver cancer showed that in a group of six patients with liver cancer (three primary and three metastatic) phenazone clearance was unchanged. Clearance of antipyrine was also reported in an increase in the AUC.

References


Acknowledgement

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Table 2 Liver function tests

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<th>Total protein 65–85 g litre⁻¹</th>
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B. Liver function tests for secondary cancer liver group

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