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Morphine and morphine-glucuronide concentrations in plasma and CSF during long-term administration of oral morphine

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Concentrations of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) were measured by h.p.l.c. in plasma and cerebrospinal fluid (CSF) samples from 16 patients with cancer receiving oral (controlled-release) morphine. There was a close correlation between plasma and CSF morphine concentrations ($r = 0.94$, $P = 0.0001$) and both correlated with drug dosage ($r = 0.61$, $P = 0.013$ and $r = 0.74$, $P = 0.0001$, respectively). M3G and M6G in plasma and CSF were correlated ($r = 0.81$ and $r = 0.82$, both $P = 0.0001$). No relationship was apparent between M plus M6G concentrations in the CSF and pain scores.

Keywords oral morphine morphine glucuronides plasma and CSF concentrations cancer pain

Introduction

After oral administration, morphine (M) is metabolised in the intestinal mucosa and the liver mainly to its 3-glucuronide (M3G) and 6-glucuronide (M6G) [1]. M6G is considered to contribute to the analgesic effectiveness of M [2], and both have been measured in plasma and CSF after different routes of M administration [3, 4, 5]. However, most of these data were obtained during short term administration and little is known about the pharmacokinetics of M and its glucuronides in plasma and CSF after long-term oral M administration [6].

This study assessed the relationships between plasma and CSF concentrations of M and its glucuronides during long-term oral administration of controlled-release M, and any association with pain scores in cancer patients.

Methods

A tunnelled intrathecal catheter for M administration was placed in each of 16 patients with cancer who had insufficient pain relief or unmanageable side-effects during treatment with oral (controlled-release) M (MS-contin®, ASTA, Diemen, The Netherlands). During this oral M treatment period (range 9–250 days, mean 57 days, median 34 days) the dosage of M was increased gradually. The final daily dosage (range 60–950 mg day^{-1}, mean 305 mg, median 200 mg) was constant for at least 3 days before placement of the catheter. All patients (nine male, seven female; age 22–68; mean 54, median 56 years) were in the preterminal stage of their life due to tumours of different origin, but had normal renal and hepatic function. Pain intensity was measured by a visual analogue scale (VAS) and clinical pain characteristics were determined according to Arnèr & Arnèr [7]. Institutional approval was given for the study and patients were included after obtaining verbal and written informed consent. Immediately before placement of the catheter, blood was drawn from a peripheral vein within 3 h of the last oral M dose. Patients were allowed to eat and drink without restriction. After placement of the catheter, 0.5–1 ml of CSF was collected, sealed in a glass tube, centrifuged and stored at −20° C until assay. M, M3G and M6G concentrations were measured using the h.p.l.c. method of Koopman-Kimenai *et al.* [8]. Interday variation in the assay was less than 10% for all analytes. The lower limits of quantitation in plasma were 52.5 nmol l^{-1} for M3G, 21 nmol l^{-1} for M6G and for M, 35 nmol l^{-1}.

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Statistics

The relationships between plasma and CSF concentrations of M and its glucuronides were examined by linear regression and Pearson correlation coefficients were calculated. A P value < 0.05 was considered to be significant.

Results

The concentration of M3G was higher than those of M6G and M in both fluids in all patients whereas the CSF/plasma correlations for M3G (r = 0.81; P = 0.0001) and M6G (r = 0.82; P = 0.0001) had slopes of 0.12 and 0.09, respectively (Table 1). The relationships between oral M dosage and plasma M concentration (r = 0.61, P = 0.013) and CSF M concentration (r = 0.74, P = 0.0001) are shown in Figure 1.

M concentrations in plasma and CSF correlated closely (r = 0.94; P = 0.0001). The sum of M6G and M concentrations in the CSF did not correlate with the VAS score.

Table 1 Mean concentration ratios (s.d., range) of morphine and its 3- and 6-glucuronides in plasma and CSF (n = 16)

Plasma	
M3G/M	29 (14, 11–52)
M6G/M	4.6 (2.8, 2–11)
M3G/M6G	6.7 (1.0, 4.6–8.7)
CSF	
M3G/M	7.3 (5.6, 1–23)
M6G/M	0.8 (0.7, 0.1–3)
M3G/M6G	9.2 (2.0, 5.6–14)
CSF/Plasma	
M	0.9 (0.3, 0.5–1.7)
M6G	0.09 (0.04, 0.03–0.20)
M3G	0.12 (0.05, 0.04–0.24)

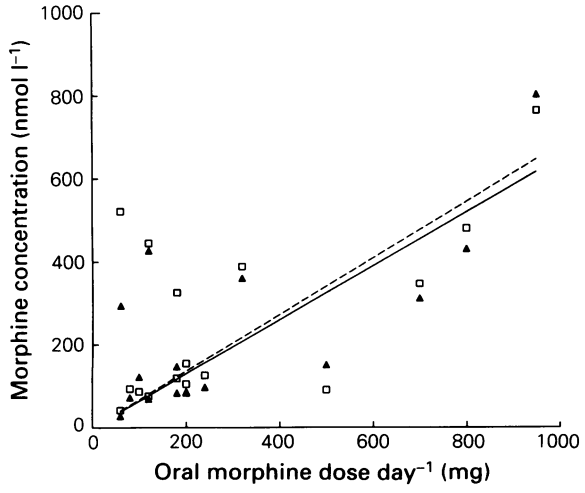

Figure 1 Relationship between plasma (□) and CSF (▲) morphine concentrations and daily oral M dose. Lines represent regression lines for plasma (——), r = 0.61, P = 0.0013 and CSF data (----), r = 0.74, P = 0.0001.

Discussion

This study confirms that there is a direct relationship between oral M dosage and the concentration of M in plasma during chronic intake of controlled-release tablets in cancer patients [9]. The scatter in Figure 1 is probably due to variation in sampling time as well as between-subject differences in the absorption and metabolism of M. CSF M and plasma M concentrations correlated closely following long-term oral administration. The plasma M3G/M and M6G/M ratios were similar to those reported previously by McQuay *et al.* [10] and Somogyi *et al.* [11] in cancer patients receiving chronic treatment with oral M.

The presence of M glucuronides in the CSF can be explained by their diffusion out of the plasma through the blood brain barrier, possibly enhanced by coiling of the M3G and M6G molecules increasing their lipophilicity [12]. As the extent of plasma binding for M3G and M6G is low (10 and 15%, respectively) [13], and the capacity of the CNS to produce M3G and M6G from M is limited [14], their plasma and CSF concentrations should eventually reach the same levels. However, an extremely slow access into the CSF can be explained both by their low lipid solubility as well as by the presence of a very low un-ionised fraction of only 0.003% at pH 7.4 [15] due to their respective pKa values (pKa of M3G 2.83 and M6G 3.23) [12]. Also, removal of M3G and M6G by CSF flow may prevent equilibration and may have attributed to the observed CSF/plasma gradient.

Because all patients had relatively severe pain, there was probably insufficient variability in pain to expect a relationship with CSF concentrations of M and M6G [7, 11]. Furthermore, CSF concentrations of M6G may not correspond to those at receptor sites, especially as tolerance to the analgesic effects of M can be expected after its long term administration.

In conclusion, this study shows a close correlation between plasma and CSF M concentrations during chronic administration of controlled-release M tablets in cancer patients. Marked M3G and M6G plasma/CSF gradients were observed.

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