

# Morphine and morphine-6-glucuronide in the plasma and cerebrospinal fluid of children

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**Aims** To measure morphine and morphine-6-glucuronide in the plasma and cerebrospinal fluid of children following a single intravenous dose of morphine.

**Methods** Twenty-nine paired samples of cerebrospinal fluid and plasma were collected from children with leukaemia undergoing therapeutic lumbar puncture. An intravenous dose of morphine was administered at selected intervals before the procedure. Concentrations of morphine and morphine-6-glucuronide (M6G) were measured in each sample. Morphine was measured using a specific radioimmunoassay (r.i.a.) and M6G was measured using a novel enzyme-linked immunosorbent assay (ELISA).

**Results** The ELISA for measuring M6G was highly sensitive. The intra- and interassay variations were less than 15%. Using a two-compartment model for plasma morphine, the area under the curve to infinity (AUC, 7143 ng ml<sup>-1</sup> min), volume of distribution (3.6 l kg<sup>-1</sup>) and elimination half-life (88 min) were comparable with those reported in adults. Clearance (35 ml min<sup>-1</sup>) was higher than that in adults. Morphine-6-glucuronide was readily synthesized by the children in this study. The elimination half-life (321 min) and AUC (35507 ng ml<sup>-1</sup> min) of plasma M6G were much greater than those of morphine.

**Conclusions** Extensive metabolism of morphine to M6G in children with cancer has been demonstrated. These data provide further evidence to support the importance of M6G accumulation after multiple doses. There was no evidence that morphine passed more easily into the CSF of children than adults.

**Keywords:** cerebrospinal fluid, children, morphine-6-glucuronide, morphine, plasma

## Introduction

It is now clear that both morphine and its metabolite morphine-6-glucuronide are as pharmacologically active in the child as in the adult. Though exact relative potency is not certain, M6G is thought to be very much more potent than morphine as an analgesic [1–8], and because of differences in the receptor interactions of the two drugs, may have fewer adverse effects [8–12].

The opioid receptors through which the two compounds act are found primarily in the central nervous system (CNS) [4, 13, 14]. A more precise estimate of their pharmacological influence might therefore be gained

by measuring concentrations in the cerebrospinal fluid (CSF), a more accurate reflection of access of the ligands to CNS opioid receptors, rather than by simply measuring plasma concentrations. It has been assumed that the blood–brain barrier of children is more easily permeable to opioids than that of adults [15], but this has not been proven.

One reason for the lack of data in children is that it is difficult to obtain appropriate samples of CSF. Children receiving treatment for leukaemia and who require repeated intrathecal chemotherapy undergo frequent lumbar puncture (LP), and morphine is often prescribed. These patients also have indwelling central venous access. In this patient group, it was possible to measure morphine and M6G in both plasma and CSF with minimal intervention.

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## Methods

### Study subjects

The study was reviewed by the Ethics Committee of the Royal Marsden Hospital and The Institute of Cancer Research. The parents of 27 patients were approached. Of these, 10 declined to participate. In all, 17 patients were studied on a total of 29 occasions. Ten samples were obtained from boys and 19 from girls. The median age was 5.5 years (range 1.4–15.9 years) and the median weight was 20.0 kg (range 9.3 kg to 54.5 kg).

### Study protocol

Patients between the ages of 1 and 18 years who were scheduled to undergo routine lumbar puncture (LP) as part of treatment for acute leukaemia were eligible. They were excluded if there was a contraindication to opioid therapy or LP. All patients had central venous access. Morphine at a dose of 250  $\mu\text{g kg}^{-1}$ , 125  $\mu\text{g kg}^{-1}$  or 60  $\mu\text{g kg}^{-1}$  was given by intravenous infusion over 15 min at selected intervals before LP was carried out under general anaesthesia. At the time of the LP a sample of CSF not exceeding 0.5 ml in volume was set aside for analysis, and a simultaneous sample of blood (not exceeding 0.5 ml  $\text{kg}^{-1}$  in volume) was removed from the central venous line. Plasma samples were immediately centrifuged and plasma and CSF were stored at  $-20^\circ\text{C}$ .

### Assay methods

**Morphine** Samples were assayed for morphine using a specific r.i.a. [16] with tritiated morphine radiolabel. The lower limit of detection for the assay is 0.28  $\text{ng ml}^{-1}$  (0.88  $\text{nmol l}^{-1}$ ).

**Morphine-6-glucuronide** Samples were assayed for M6G using an antigen coated competitive enzyme-linked immunosorbent assay (ELISA) which was an adaptation of the r.i.a. previously described [17]. Ninety-six well microtitre plates (Dynatech Immulon 2) were coated with aminobutylnormorphine-6 glucuronide ovalbumin conjugate (0.05  $\mu\text{g ml}^{-1}$ , 150  $\mu\text{l}$ /well in 70 mM sodium barbitone) for 150 min at  $37^\circ\text{C}$ . After washing three times with 0.01% Tween20/water, 150  $\mu\text{l}$  5% lactose was added to each well. The plates were dried and stored at  $4^\circ\text{C}$  with desiccant. Under these conditions the plates were stable for eight weeks.

The plates were washed before use. Antiserum (diluted 1:30 000), standard M6G (0.01–500  $\text{ng ml}^{-1}$ ), quality controls and samples were diluted in PBS buffer with gelatin and Tween 20 (37 mM NaCl, 8 mM  $\text{Na}_2\text{HPO}_4$ , 2.7 mM KCl, 1  $\text{g l}^{-1}$  gelatin, 0.1  $\text{g l}^{-1}$  thiomersal and 0.1% Tween 20). Non-specific binding and zero standard

controls ( $B_0$ ) were included on each plate and all standards, samples and controls were assayed in duplicate. Plates were incubated for 1 h at  $37^\circ\text{C}$ . Antibodies bound to the plate were visualized by incubation with goat antirabbit IgG-horseradish peroxidase conjugate (Sigma) for 1 h and subsequent reaction with tetramethyl benzidine/hydrogen peroxide substrate. After acidification the colour was read at 450 nm. Concentration of M6G was determined from standard curves using a smoothed spline data reduction program (RIASMART, Canberra-Packard).

Specificity of the antisera was as previously described [17]. Additionally, morphine-3,6, diglucuronide was tested and showed no significant cross-reaction (0.008%).

Theoretical assay sensitivity, defined as a two-standard deviation fall from  $B_0$ , was 0.04  $\text{ng ml}^{-1}$ . Plasma samples were diluted at least 20 times to eliminate matrix effects (detection limit 0.8  $\text{ng ml}^{-1}$ ). There was no matrix effect with CSF (detection limit 0.04  $\text{ng ml}^{-1}$ ). Interassay variation of the standards was 7.5%. Sample interassay variation was 14.5% ( $12.4 \pm 1.8 \text{ ng ml}^{-1}$ ). Mean recovery of 50  $\text{ng ml}^{-1}$  M6G added to plasma was 102.5% (s.d. 8.6,  $n=7$ ). As reported previously for the r.i.a. [17], addition of increasing concentrations of morphine and M3G had no effect on the recovery of M6G.

Comparative analysis of the same samples using h.p.l.c. [18] showed that there was a linear relationship across the range of results ( $y=1.74x-3.3$ ,  $r=0.93$ ,  $n=49$ ). The relationship of h.p.l.c. data with ELISA data was thus very similar to the relationship of h.p.l.c. data with r.i.a. [17].

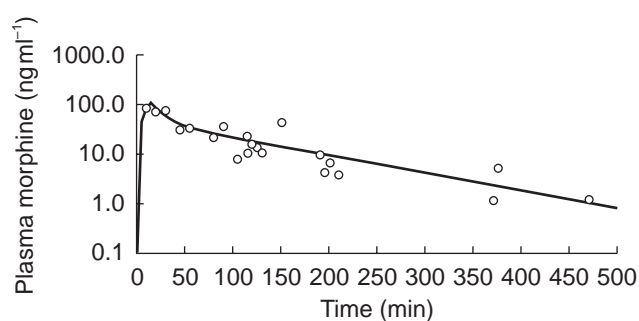
### Pharmacokinetic analysis

Morphine data were standardized to a dose of 250  $\mu\text{g kg}^{-1}$  and analysed as though all came from a single patient using WinNonLin, pharmacokinetic model 10. This was a two-compartment, i.v. infusion model (over 15 min), with macro-constants, no lag time and  $1/y^2$  error weighting. The equation of the curve was in the form  $C_t = A(e^{-\alpha t} - e^{-\alpha t^*}) + B(e^{-\beta t} - e^{-\beta t^*})$  where  $t^*$  = infusion time (min) Initial estimates were  $A = 1000$ ,  $\alpha = 0.03$ ,  $B = 0.07$ ,  $\beta = 0.01$ .

A noncompartment model was used to estimate AUC and terminal elimination half-life ( $\lambda_z$ ) for M6G in plasma. A two-compartment model (Figure 1) fitted the data for plasma morphine. Correlation between observed and predicted concentrations was 0.9213 (Akaike and Schwartz Criteria 105 and 103, respectively).

## Results

Pharmacokinetic parameters for plasma and CSF morphine and CSF are shown in Table 1. The maximum



**Figure 1** Concentration of morphine in plasma ( $\text{ng ml}^{-1}$ ) following administration of morphine to children with leukaemia. — predicted concentrations,  $\circ$  = observed concentrations.

**Table 1** Comparison of pharmacokinetic parameters of plasma M6G and morphine (all data standardised to  $250 \mu\text{g kg}^{-1}$ ).

	M6G	Morphine
$t_{\text{max}}$ (min)	337	9.9
$C_{\text{max}}$ ( $\text{ng ml}^{-1}$ )	130	106
AUC ( $\text{ng ml}^{-1} \text{min}$ )	35 507	7143
Clearance ( $\text{ml min}^{-1}$ )	7	35
Terminal $t_{1/2}$ (min)	321	88
Volume of distribution at steady state ( $\text{l kg}^{-1}$ )	Not calculated	3.6

CSF concentration, and time to maximum concentration were, respectively,  $16 \text{ ng ml}^{-1}$  and 125 min for morphine, and  $34 \text{ ng ml}^{-1}$  and 470 min for M6G.

In the first 30 min after intravenous morphine, plasma concentrations of morphine were more than 10 times those in CSF. After 2 h, plasma and CSF concentrations were approximately equal. The plasma concentration of M6G generally exceeded that of CSF (Figure 2b). Initially the ratio was high, reaching a maximum of nearly 500:1 after 105 min, but then declined until four hours, after which plasma and CSF concentrations declined in parallel such that plasma concentrations remained approximately 10 times those in the CSF.

In the plasma, morphine concentrations initially exceeded those of the metabolite. The ratio fell over the course of the first 1–2 h, whereafter plasma M6G exceeded morphine. In the CSF, concentrations of morphine exceeded those of the metabolite at all points where measurements of both were available. Morphine appeared to be eliminated more quickly from CSF than M6G (Figure 2d).

## Discussion

The ELISA used in this study was a nonradioactive adaptation of a previously described immunoassay [17]. It was particularly suited to this paediatric study, where sample volumes were low, by virtue of its exquisite

sensitivity. Specificity and correlation with h.p.l.c. were similar to those described for the r.i.a.

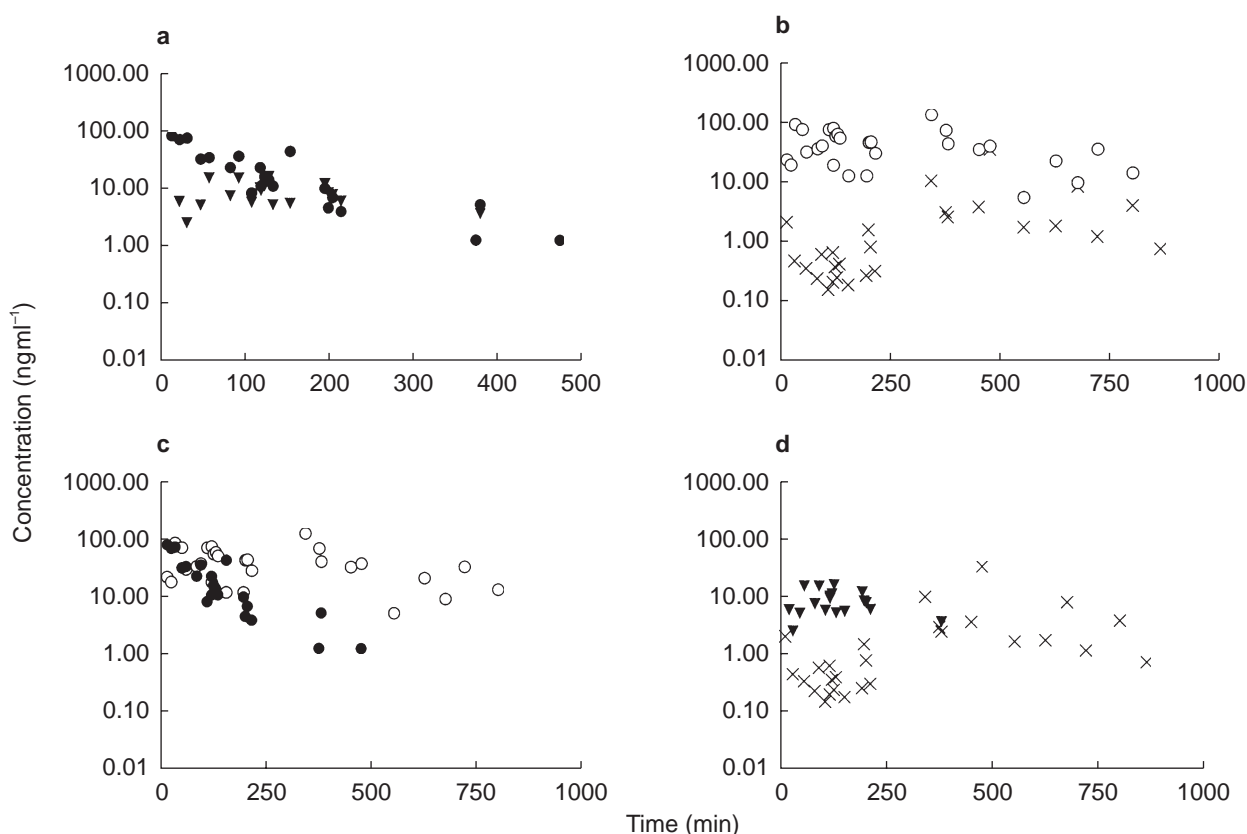
### Morphine in plasma and CSF

This study suggests that the plasma kinetics of morphine (Table 1, Figure 1) in children over 1 year old are little different from those reported in adults. As in other studies in children [19–28], the mean clearance of morphine was rather higher than that in adult studies [29–32], but half-life, volume of distribution and AUC were all similar to those of adults. Since it was possible to standardize the data by weight and dose and obtain a credible pharmacokinetic profile, the volume of distribution does not appear to alter significantly through childhood after a year old. This supports evidence from other paediatric studies [27], and suggests that in calculating a dose for children, the current extrapolation on which paediatric doses are based (the same dose per kg weight as that of an adult) is appropriate. The elimination half-life, from this study, is also similar to that of adults, suggesting that the dosage interval used in healthy adults also remains appropriate for children over a year old. However, these data do not exclude the possibility that a child's response to a given plasma concentration of morphine is different from that of an adult.

Previous studies of morphine kinetics in children [19, 22, 24, 25, 27, 33–35] have used one-, two- or three-compartment models. Our data were better fitted by a two-compartment model than a single-compartment model (data not shown).

Modelling based on population pharmacokinetics might have been considered preferable to standardization of the morphine data and analysis as though from a single patient. However, such analysis requires prior knowledge of the study population that is not available for children, and although numbers of patients in this study compared favourably with other paediatric studies, they are still smaller than those ideally required for population analyses. Furthermore, because the timing of sample collection was constrained by clinical expediency, the number of points for each patient was small and there were few data at each individual time point. There was also insufficient prior knowledge for detailed modelling of plasma metabolite data. A noncompartment approach was therefore used to estimate AUC and elimination half-life.

This study provided no evidence that the blood–brain barrier of children over 1 year old is more permeable to morphine than that of an adult. The ratio of plasma:CSF concentrations of morphine at equilibrium after 2 h was 1:0.9, similar to that of adults [32, 36–38]. The time taken to reach maximum concentration in the CSF was slightly longer in one adult study [32], but this is probably the result of using intramuscular rather than intravenous



**Figure 2** Comparison of (a) morphine concentrations in plasma and CSF. (b) morphine-6-glucuronide concentrations in plasma and CSF. (c) morphine and M6G concentrations in plasma. (d) morphine and M6G concentrations in CSF. ● = plasma morphine, ▼ = CSF morphine, ○ = plasma M6G, × = CSF M6G.

morphine in that study. An equilibrium was reached rapidly, at which CSF and plasma concentrations of morphine were approximately equal.

#### *Morphine-6-glucuronide in plasma and CSF*

The capacity to glucuronidate morphine has been shown in the 15-week fetus [39] and in preterm and full-term neonates [26, 33, 34, 40–43]. In this study, M6G was detectable in the earliest plasma and CSF samples, analysed 11 min after morphine.

The time taken for the plasma concentration of M6G to exceed that of morphine in this study (2 h) was similar to that in an adult study [11]. However, maximum plasma concentration of M6G, AUC for M6G in plasma and the AUC ratio of plasma M6G:morphine (molar ratio 3:1) were all significantly greater in this study than in comparable adult studies [11, 44]. This is probably due to methodological differences since both adult studies were over a shorter period and used h.p.l.c., which is less sensitive than immunoassay but also less subject to variability. Another factor may have been that all the children in this study were anaesthetized. It has been shown in adults [45] that peak concentrations and AUC

of M6G in plasma are greater in anaesthetized patients. An alternative explanation is that there is a real difference between adults and children in the capacity to generate or to eliminate M6G; this possibility should be addressed in further paediatric studies.

Despite being less lipophilic than morphine, M6G was detected at 11 min, in the first CSF sample examined. The maximum concentration of M6G occurred much later than that of morphine (470 min, compared with 125 min), but was of comparable magnitude. Clinical experience suggests that the maximum benefit, as well as the most severe adverse effects, of an intravenous dose of morphine are seen well before the time to peak CSF concentration of M6G in this study. Such effects coincide rather with the time taken to peak concentration of morphine in CSF (125 min). This suggests that the effectiveness of a single intravenous dose of morphine is mediated by morphine itself, rather than by M6G. It has been argued [46–49] that after multiple doses the clinical effects are those of accumulating M6G. If adverse effects are more related to morphine than to M6G [8–12], these findings would explain the observation that adverse effects are most severe during the first 2 days of ongoing opioid therapy [50].

## Conclusions

The data from this study suggest that the plasma kinetics of morphine in paediatric cancer patients over 1 year old are little different from those of healthy adults. The study is the first to measure morphine and M6G simultaneously in the CSF of children; the data indicate that the access of morphine and its active metabolite M6G into the CSF of children is similar to that seen in adults. There is no evidence to support the belief that the child's blood-brain barrier offers less resistance to the passage of opioids than that of an adult.

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