STUDIES ON MORPHINE DISPOSITION: INFLUENCE OF GENERAL ANAESTHESIA ON PLASMA CONCENTRATIONS OF MORPHINE AND ITS METABOLITES

J. W. SEAR, C. W. HAND, R. A. MOORE AND H. J. McQUAY

General anaesthesia and surgery cause alterations in hepatic and renal blood flow when compared with the awake patient. Anaesthesia may also cause changes in peripheral blood flow distribution. Thus anaesthesia may influence perioperative drug disposition by three separate effects: on drug distribution, on hepatic blood flow and on drug elimination. Tranquilli and colleagues [1] have shown nitrous oxide–halothane anaesthesia in swine caused changes in peripheral blood flow, especially within the splanchic circulation, fatty tissues, skeletal muscle and skin. Furthermore, general anaesthesia also causes reduction in renal blood flow, and hence a decrease in the glomerular filtration rate. Thus elimination of drug metabolites may also be affected by general anaesthesia.

Morphine is metabolized principally in man by biotransformation to two glucuronides which are eliminated by renal filtration. Morphine-3-glucuronide (M3G) is pharmacologically inactive, while morphine-6-glucuronide (M6G) has been shown to be analgesically active when injected intracerebrally and subcutaneously in mice [2]. M6G is known to enter the central nervous system in man after single doses of morphine 10 mg [3]. There is also growing evidence to suggest that increased plasma concentrations of M6G in man may account for the increased efficacy of the opioid when given to patients with impaired renal function.

There are no studies to date investigating the influence of general anaesthesia on morphine and its metabolites in man. The present study has compared, therefore, the disposition of the parent compound and its two main metabolites in two groups of patients: one awake and receiving the opioid for relief of chronic non-cancer pain; the second receiving morphine as part of balanced anaesthesia for lower abdominal or body surface surgery.

SUMMARY

The kinetics of morphine were studied during balanced anaesthesia in 10 patients undergoing lower abdominal or body surface surgery, and compared with those obtained in nine awake patients receiving morphine i.v. for the relief of chronic non-cancer pain. All patients received morphine sulphate pentahydrate 10 mg i.v. over 30 s. Venous blood samples were collected for up to 180 min, and plasma concentrations of morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) assayed by a differential radioimmunoassay technique. There were no differences between groups with respect to the elimination half-life (awake group: 207 min; anaesthetized group: 153 min), volume of distribution at steady state (awake: 147 litre; anaesthetized: 128 litre), or clearance (awake: 587 ml min⁻¹; anaesthetized: 766 ml min⁻¹). Peak concentrations of M3G were similar in the two groups, but the peak concentration of M6G was greater in the anaesthetized patients. The AUC for M3G and M6G (0–180 min) also were greater in the anaesthetized patients, presumably as a result of decreases in renal blood flow and glomerular filtration rate during halothane anaesthesia.
PATIENTS AND METHODS

Nineteen patients (ASA I or II, aged 36–60 yr, weights 50.3–89.4 kg) were studied after giving their informed consent to participation in the programme, which was approved by the local hospital Ethics Committee.

Nine patients undergoing treatment for chronic non-cancer pain received morphine sulphate pentahydrate (Evans Medical, Beaconsfield, Bucks) 10 mg given i.v. over 30 s in 10 ml of normal saline (0.154 mol litre⁻¹). None of these patients was receiving other drugs known to alter hepatic blood flow or hepatic metabolizing enzyme ability; none had previously received morphine or other opioids.

The other 10 patients were undergoing lower abdominal or body surface surgery. Premedication comprised diazepam 10–15 mg by mouth, 90 min before induction of anaesthesia with a sleep dose of thiopentone 4–5 mg kg⁻¹; the trachea was intubated following neuromuscular blockade with alcuronium 0.25 mg kg⁻¹. Anaesthesia was maintained with 67% nitrous oxide in oxygen supplemented by halothane (up to 1%). When stable haemodynamics had been achieved after induction, morphine sulphate pentahydrate 10 mg was given i.v. over 30 s. At the end of surgery, residual neuromuscular blockade was antagonized with atropine and neostigmine. In both study groups, arterial pressure and heart rate were monitored continuously, as was the electrocardiogram in those patients undergoing surgery.

Venous blood samples (2 ml) were collected from a cannula in the arm contralateral to the site of drug administration before injection of morphine and at 1, 2, 5, 7, 10, 15, 30, 45, 60, 90, 120, 150 and 180 min after injection. Samples were taken into lithium-heparin tubes and the plasma separated by centrifugation and stored at −20 °C until assayed for morphine and the two metabolites by a differential radioimmunoassay technique described by Hand and colleagues [4]. The assay for morphine has a coefficient of variation of 5–10% over the concentration range reported here, a sensitivity of 10 nmol litre⁻¹; and cross reactivity with M3G, M6G and normorphine of 0.07%, 0.1% and 0.02%, respectively.

Kinetic parameters were calculated using model-independent methods. The areas under the concentration–time curve (AUC₀⁻¹₈₀) for morphine, M3G and M6G were determined using the linear trapezoidal rule. The extrapolated AUC₁₈₀⁻∞ for morphine was calculated from the concentration at 180 min and the elimination rate constant. Other kinetic parameters for morphine (systemic clearance (Clₚ); apparent volume of distribution during the elimination phase (Vdarea); volume of distribution at steady state (Vdss); mean residence time (MRT)) were determined from the AUC and its first moment, AUMC.

Plasma concentration data and AUC for morphine, M3G and M6G were compared between the two groups using the Mann–Whitney U test, as were the derived kinetic parameters. Data are expressed throughout as the mean (SD), and range.

RESULTS

The patients in the two study groups were comparable for age and weight. The duration of anaesthesia was 91.8 (19.9) min. During anaes-

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**Table 1. Plasma morphine concentrations (nmol litre⁻¹) in awake and anaesthetized patients receiving morphine sulphate pentahydrate 10 mg i.v. Data shown as mean (SD) [range]**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Awake (n = 9)</th>
<th>Anaesthetized (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2436 (2130) [537–5555]</td>
<td>2777 (1029) [1948–4248]</td>
</tr>
<tr>
<td>2</td>
<td>1092 (907) [463–3146]</td>
<td>1429 (328) [883–1919]</td>
</tr>
<tr>
<td>5</td>
<td>357 (120) [150–572]</td>
<td>427 (116) [347–574]</td>
</tr>
<tr>
<td>7</td>
<td>261 (58) [174–357]</td>
<td>310 (66) [224–423]</td>
</tr>
<tr>
<td>10</td>
<td>227 (50) [147–283]</td>
<td>275 (61) [171–392]</td>
</tr>
<tr>
<td>15</td>
<td>168 (50) [130–289]</td>
<td>199 (36) [147–246]</td>
</tr>
<tr>
<td>30</td>
<td>147 (26) [113–181]</td>
<td>128 (35) [96–184]</td>
</tr>
<tr>
<td>45</td>
<td>146 (46) [99–235]</td>
<td>102 (16) [79–124]</td>
</tr>
<tr>
<td>60</td>
<td>114 (20) [84–145]</td>
<td>95.3 (21) [63.2–134]</td>
</tr>
<tr>
<td>90</td>
<td>99 (30) [58–149]</td>
<td>79.9 (19) [48.9–108]</td>
</tr>
<tr>
<td>120</td>
<td>86.5 (14) [66–111]</td>
<td>70.9 (20) [50–115]</td>
</tr>
<tr>
<td>150</td>
<td>91.7 (29) [55–144]</td>
<td>72.7 (31) [44–130]</td>
</tr>
<tr>
<td>180</td>
<td>80.7 (27) [55–142]</td>
<td>53.5 (18) [32–85]</td>
</tr>
</tbody>
</table>
TABLE II. Derived kinetic parameters for morphine, and concentration–time data for morphine-3-glucuronide and morphine-6-glucuronide in awake and anaesthetized patients. Data shown as mean (SD) [range]. *P < 0.05; **P < 0.025; ***P < 0.006

<table>
<thead>
<tr>
<th></th>
<th>Awake patients</th>
<th>Anaesthetized patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination half-life</td>
<td>207.7 (73.8) [112.1–318.3]</td>
<td>153.1 (60.6) [79.1–270.8]</td>
</tr>
<tr>
<td>MRT (min)</td>
<td>274.0 (110.5) [154.7–429.0]</td>
<td>189.4 (93.0) [85.1–318.1]</td>
</tr>
<tr>
<td>$C_l$ (ml min$^{-1}$)</td>
<td>587.3 (192.3) [289.2–955.5]</td>
<td>766.1 (212.2) [406.5–1121.1]</td>
</tr>
<tr>
<td>$Vd_{BS}$ (litre)</td>
<td>146.8 (38.6) [98.6–205.7]</td>
<td>128.1 (31.6) [54.8–166.8]</td>
</tr>
<tr>
<td>$Vd^{ss}$ (litre)</td>
<td>161.1 (40.2) [126.6–235.6]</td>
<td>157.2 (42.1) [87.9–212.3]</td>
</tr>
</tbody>
</table>
| Morphine-3-glucuronide
| $C_{max}$ (nmol litre$^{-1}$) | 568 (189) [232–797] | 694 (213) [489–1236]       |
| $T_{max}$ (min)      | 59 (46) [20–150]     | 51 (30) [30–120]             |
| AUC (nmol litre$^{-1}$ min) | 69295 (26184) [29496–105904] | **104486 (24417) [76296–159230] |
| Morphine-6-glucuronide
| $C_{max}$ (nmol litre$^{-1}$) | 64.4 (33.0) [11.5–103.7] | * 102.4 (44.4) [54.5–181.4] |
| $T_{max}$ (min)      | 51 (33) [5–120]      | 53 (19) [30–90]              |
| AUC (nmol litre$^{-1}$ min) | 7114 (4128) [1679–12932] | **13207 (6306) [6805–26344] |

Fig. 1. Area under concentration–time curves from 0 to 180 min for morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), and morphine clearance in awake patients (black columns) and anaesthetized patients receiving morphine sulphate pentahydrate 10 mg i.v. Data shown as mean and SD. *P = 0.025; **P = 0.006 (Mann–Whitney U test).

However, there were differences between the groups with respect to the time to peak concentration ($T_{max}$) and the peak concentration ($C_{max}$) for the two glucuronides in addition to the AUC$_{0–180}$ for M3G and M6G (fig. 1). The AUC$_{0–180}$ for M3G in awake subjects was 69295 (26184) nmol litre$^{-1}$ min, and 104486 (24417) nmol litre$^{-1}$ min in the anaesthetized patients ($P = 0.006$). Similar differences were found for M6G: 7114 (4128) nmol litre$^{-1}$ min in the awake patients, and 13207 (6306) nmol litre$^{-1}$ min in the anaesthetized group ($P = 0.025$). $C_{max}$ (M6G) was significantly greater in the anaesthetized patients ($P < 0.05$).
Anaesthesia increased the plasma M3G AUC to plasma morphine AUC ratio (0–180 min) from 2.9 (1.3) to 4.3 (0.6) \((P = 0.01)\), but had no significant effect on the plasma M6G AUC to plasma morphine AUC ratio over the same period: 0.32 (0.21) and 0.54 (0.20), respectively.

**DISCUSSION**

Although many studies have described the influence of anaesthesia upon parent drug disposition, there are few where the authors have measured drug metabolites and investigated the effects of general anaesthesia upon their elimination.

In the absence of surgery, inhalation anaesthesia causes a decrease in cardiac output and liver blood flow \([5, 6]\). In addition, nitrous oxide also decreases splanchnic blood flow \([7, 8]\). In the presence of surgery, different authors have reported varying effects on hepatic blood flow. Surgical laparotomy usually resulted in decreased hepatic arterial blood flow \([9–11]\). Using radio-labelled colloidal gold, Gelman \([12]\) showed greater decreases in liver blood flow during upper abdominal compared with lower abdominal or body surface surgery in patients receiving 0.5–1.0% halothane to supplement nitrous oxide in oxygen. However, if indocyanine green (ICG) clearance is used as an indirect index of hepatic blood flow, then data from Nancarrow and colleagues \([13]\) and Cousins and colleagues \([14]\) would suggest halothane anaesthesia in concentrations of 0.35–0.5% to supplement nitrous oxide in oxygen has little effect on liver blood flow. On the other hand, Gelman, Fowler and Smith \([15]\) have demonstrated that ICG clearance decreased progressively with increasing doses of halothane. However, these results did not correlate with the observed measured flow changes, suggesting that the hepatic extraction ratio of ICG changed during halothane anaesthesia.

In the present study, general anaesthesia did not inhibit the elimination of morphine. This is in agreement with the data of Merrell and colleagues \([16]\), who were unable to demonstrate any effect of halothane anaesthesia on the formation of M3G from morphine in dogs. Both Mather and colleagues \([17]\) and Behne and colleagues \([18]\) have also shown in sheep an absence of any significant effect of volatile anaesthetic agents on the clearance of lignocaine and midazolam, although this is in contrast to the findings of Bentley, Glass and Gandolfi in man \([19]\). In addition, there have been reports of significant decreases in systemic clearance of fentanyl, systemic and intrinsic clearance of propranolol and systemic clearance of verapamil during halothane anaesthesia in dogs \([20–22]\).

Mean clearances of morphine in our anaesthetized and awake patient groups were comparable to those reported in the study of Aitkenhead and colleagues \((11.5 \text{ ml kg}^{-1} \text{ min}^{-1})\), in which a similar blood sampling procedure was adopted, but morphine concentrations were assayed by HPLC \([23]\). The elimination half-life in both patient groups was similar to that obtained by Aitkenhead; in both studies the limited duration of sampling limited the accuracy of this half-life, tending to underestimate the true value. The large variability in morphine clearance and half-life in both the anaesthetized and awake patient groups may be related to a number of factors: patient age and sex, other intercurrent medication, renal function, etc. Similar dispersion of data may be seen in the patients studied by Aitkenhead \([23]\), and the other studies he cited, and it is unlikely, therefore, that the variability in our patients may be explained solely on the basis of assay methodology.

Of greater interest than the unaltered elimination of morphine was the increased AUC for both M3G and M6G in the anaesthetized patients. There is a decrease in renal blood flow and glomerular filtration rate during halothane anaesthesia in man \([24, 25; \text{Groves and Rosen, European Academy of Anaesthesiology, Ghent}]\) which, in the presence of normal hepatic drug metabolism, leads to increased plasma concentrations of renally excreted metabolites.

Published data \([26]\) for the elimination half-life of M3G in healthy patients reveal values between 2.4 and 6.7 h and hence are in excess of the half-life of the parent compound in this study. The only estimate for the half-life of M6G is approximately 2 h following a single i.v. dose of M6G 1 mg/70 kg body weight \([27]\). The short sampling time in the present study has precluded an estimate of the half-life of these two metabolites in each patient group. However, the increased AUC for both in the anaesthetized patients suggests prolongation of the half-life and, hence, prolongation of any dynamic effects of an active metabolite. The percentage increase in AUC for M3G and M6G in the anaesthetized patients is approximately 80%; studies on the influence of anaesthesia on renal blood flow and hence the glo-
merular filtration rate suggest the latter decreases by a comparable extent (between 30 and 50%) [24, 25]. Other mechanisms for the increased AUC might involve reduced biliary excretion of the glucuronides, but the present study was not designed to answer this question.

Inspection of the data for M3G and M6G does not suggest any relationship between the duration of anaesthesia and the AUC(0–180) for each glucuronide, or a relationship between the C(max) or T(max) for either M3G or M6G and duration of anaesthesia. Thus we cannot comment on whether or not the impaired elimination of the glucuronides was confined solely to the intraoperative period. However, Selby and colleagues [28], using a chronically cannulated sheep model, have shown a persistent effect of anaesthesia on renal function extending into the early postoperative period.

Morphine-6-glucuronide binds rapidly and avidly to opioid receptors in bovine brain, while its analgesic potency in rodents is greater than that of morphine after either subcutaneous or intracerebral injection [2, 29]. Pasternak and colleagues [30] have reported that M6G is a powerful mu agonist, with a binding affinity similar to that of the parent compound, but with a 20-fold increased potency. In addition, increased plasma concentrations of M6G in patients with renal failure may be one cause of the exaggerated opioid responses following morphine [31, 32]. It is not clear, in the healthy patient undergoing general anaesthesia, if the increased AUC for M6G (0–180 min) contributes to an enhanced analgesic effect for a given dose of morphine. However, the influence of general anaesthesia on morphine disposition may be a more significant factor in patients with pre-existing impaired renal function.

REFERENCES


29. Christensen CB, Jorgensen LN. Morphine-6-glucuronide has high affinity for the opioid receptor. *Pharmacology and Toxicology* 1987; 60: 75–76.

