Title : MORPHINE ANESTHESIA IN PATIENTS WITH LIVER FAILURE

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INTRODUCTION. Morphine (M) is administered in large doses for anesthetic purposes. M "anesthesia" is used for patients with abnormal liver function in order to avoid volatile anesthetics which may be hepatotoxic. One concern about this use of M is the prolongation of its duration of action, because the primary mechanism of M elimination in man is hepatic biotransformation to morphine-glucuronide.[1]

METHODS. Five patients with end-stage liver disease were studied during the intraoperative period of homograft liver transplantation. They were informed and gave their written consent to this institutionally approved study. A single dose of M (0.67 ± .04 mg/kg) was administered iv at a rate of 5-10 mg/min. Arterial blood was sampled intermittently and urine collected continuously over the next 24 hours. Plasma and urine samples were analyzed specifically for unchanged M and for total M (i.e., unchanged M and its metabolites).[2] In addition, some urine samples were incubated with β-glucuronidase in order to estimate specifically their content of morphine-glucuronide. The diseased liver was removed within the first 2 hours and revascularization of the donor liver occurred 6 or more hours after M administration.

RESULTS. Plasma concentrations of unchanged M ranged from 45 to 308 ng/ml in samples taken 2 hours after the iv dose. More than 98% of the dose left the plasma compartment by 2 hours. The subsequent decline of M levels was much slower with an apparent half-time in excess of 5 hours between 6 and 12 hours after M injection (figure). M metabolites, calculated as the difference between unchanged and total M, were evident 2 hours after injection and their proportion increased progressively with time both before and after revascularization of the newly transplanted liver. Urine collected over the first 6 hours following M administration and before revascularization of the donor liver contained 32 ± 7% of the administered dose predominately as conjugated metabolites (i.e., 72-90% of the total M in urine). Incubation of selected urine samples with β-glucuronidase indicated that essentially all of the conjugated metabolites were glucuronides.

DISCUSSION. The initially rapid clearance of 98% of the iv dose of M from plasma presumably resulted from extensive uptake of the unchanged drug by body tissues. In this regard, patients with liver failure resembled normal men in which the distributive phase of M disposition was essentially complete within 2 hours.[2,3] Nevertheless, the absolute levels of M in plasma 2 hours after injection in liver-failure patients were higher than the 50 ng/ml estimated for a 0.7 mg/kg dose from studies in patients with normal liver function.[2-4] These higher plasma levels and the slower subsequent clearance of M from plasma are to be expected in the absence of hepatic function. The notable finding of this study is that M metabolism, especially glucuronide-conjugation, occurred in spite of liver failure. This observation indicates that there are nonhepatic sites of M biotransformation in man. It also means that the anesthesiologist can anticipate eventual recovery from the effects of M administered to such patients. Although it is not possible to make precise estimates of dosage requirements from this study, the data suggest that the initial dose of M will be somewhat less than for patients with normal liver function. The need for maintenance doses will be markedly reduced both in amount and frequency of administration.

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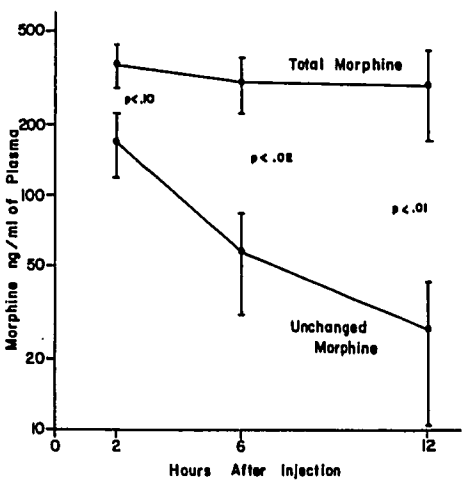

Figure: Plasma concentrations of unchanged and total M in patients undergoing liver transplantation. P values were determined by Student's t-test (n=5).