DETERMINANTS OF SYSTEMIC AVAILABILITY OF MORPHINE AND BUPRENORPHINE IN THE RAT

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Oral administration of morphine or certain of its analogues, like buprenorphine, results in low systemic blood concentrations of parent drug. This poor systemic availability precludes the use of the oral route for these narcotic analgesics. The purpose of this investigation was to identify the source(s) of pre-systemic losses of morphine (M) and buprenorphine (B) using the rat as an animal model.

The disposition of [^{3}H]-morphine (0.084 mg/kg) and [^{3}H]-buprenorphine (0.110 mg/kg) was investigated in 48 female Sprague-Dawley rats (200-250 g). Each animal received one of the two drugs by either the intra-arterial (ia, via the carotid artery), intravenous (iv, via the jugular vein), hepatic portal vein (hpv) or oral (id, administration into the duodenal lumen) route. Blood samples were removed over a 5 hour period after dosing and analysed for parent drug and conjugates following selective extraction. The mean area under the plasma concentration-time curve (AUC) for each drug after administration by each of the 4 routes are shown with the standard deviation for n = 6 in the Table.

Area under the plasma concentration-time curve (μg/ml min) for Morphine and Buprenorphine after administration by different routes

Route	After M admin	After B admin
ia	1.78 ± 0.29	3.86 ± 0.18
iv	1.60 ± 0.35	3.96 ± 0.23
hpv	0.82 ± 0.19	1.10 ± 0.21
id	0.60 ± 0.11	0.54 ± 0.03
Variance due to routes	1.995	9.690
Residual variance	0.063	0.033

One way analysis of variance showed the influence of route of administration was highly statistically significant ($p<0.001$) for both M and B. The overall oral availability, F (AUC ratio of id/ia) was 0.34 for M and 0.14 for B. Separate studies involving urinary and biliary excretion established that absorption from the gastrointestinal lumen was complete. Therefore the low F was a result of first pass metabolism. There are 3 potential sites for first pass metabolism which an orally administered drug must pass prior to reaching the systemic circulation - the gastrointestinal mucosa, liver and lung. These organs are arranged in series and therefore F is equal to product of the fractions of the dose escaping metabolism by the gastrointestinal tract (f_G), liver (f_H) and lung (f_L). The contribution of each organ may be factored out by comparison of AUC for the 4 routes (Cassidy and Houston, 1980) - f_L (AUC ratio of iv/ia) for M = 0.89 (NS) and the B = 1.03 (NS); f_H (AUC ratio of hpv/iv) for M = 0.51 ($p<0.05$) and for B = 0.28 ($p<0.05$); f_G (AUC ratio of id/hpv) for M = 0.74 (NS) and for B = 0.49 ($p<0.05$). The Student-Newman-Keuls test for multiple comparisons (Sokal and Rohlf, 1969) was used to assess the significance of each site of metabolism.

Hence the marked difference in the extent of first pass metabolism for M and B would appear to be due to both hepatic and extrahepatic enzyme activity. The role of the gastrointestinal mucosa is substantial for B but not M.

Cassidy, M.K. and Houston, J.B. (1980) J. Pharm. Pharmac. 32: 57-59.
Sokal, R.R. and Rohlf, F.J. (1969) Biometry. p. 235-246, Freeman and Co., San Francisco.

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