THE ALIMENTARY ABSORPTION OF DIAMORPHINE AND MORPHINE IN MAN AS INDICATED BY URINARY EXCRETION STUDIES

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1 Urine was collected over 24 h from 40 patients with advanced malignant disease who had received a known four-hourly oral dose of either diamorphine or morphine in an elixir or of diamorphine by injection for at least 3 days.

2 Samples were assayed for total urinary morphine (free and conjugated) by gas-liquid chromatography.

3 The percentage of the administered dose recovered as morphine was:
   (a) diamorphine hydrochloride by injection: 70% (s.d. 25)
   (b) diamorphine hydrochloride by mouth: 77% (s.d. 27)
   (c) morphine sulphate by mouth: 56% (s.d. 21)

4 It is suggested that diamorphine hydrochloride is completely absorbed by the gastro-intestinal tract but that morphine sulphate is only some two-thirds absorbed.

Introduction

Throughout the United Kingdom elixirs containing either diamorphine or morphine are used to relieve pain in advanced malignant disease. As part of a comprehensive evaluation of such preparations, it was decided to study the urinary excretion of morphine in a group of patients receiving diamorphine or morphine by mouth every 4 hours. Previous investigation of the urinary excretion of morphine in the non-addict has been limited to recovery following a single dose of injected morphine (Oettel, 1950; Elliott, Tolbert, Adler & Anderson, 1954; Paerregaard, 1957). We record here the results of our study and discuss them in relation to absorption from the gastro-intestinal tract. A quantitative assessment of the alimentary absorption of these preparations has not previously been reported.

Method

All investigations were carried out in patients with advanced malignant disease undergoing treatment at St Christopher’s Hospice. In no case was any procedure carried out unless indicated clinically. Urine was collected over 24 h from 18 patients receiving known four-hourly doses of orally administered diamorphine hydrochloride and from 10 receiving morphine sulphate. In addition, for comparative purposes, urine was collected from 12 patients receiving diamorphine hydrochloride by subcutaneous or intramuscular injection.

Of the 40 patients, 28 were female, 12 of whom had carcinoma of the breast. Twelve patients had carcinoma of the colon or rectum, three had carcinoma of the lung and two a primary hepatoma. There was histological or clinical evidence of metastatic involvement of the liver in four cases. None had carcinoma of the stomach or small bowel. The three groups were comparable in terms of sex and primary sites. Median survival from the time of urine collection was 4 weeks, ranging from less than 2 days to more than 6 months. It was greatest in the oral morphine group (7 weeks) and least in the injected diamorphine group (2 weeks).

By mouth, either diamorphine hydrochloride or morphine sulphate was given in an elixir which also contained alcohol, cocaine and either prochlorperazine or chlorpromazine. On account of its limited shelf life, elixirs containing diamorphine were discarded if not used within 2 weeks of preparation (Twycross, 1974). For parenteral administration, freeze-dried diamorphine hydrochloride was used, prepared in ampoules and dissolved in sterile distilled water.
immediately prior to injection. Other drugs were prescribed as indicated.

All the patients had been on a steady dose for at least 3 days before the urine collection, the majority for more than 2 weeks. With the exception of four men, all had a catheter in situ. Urine volume was measured and samples for the determination of morphine kept at −20°C. Subsequently, the samples were incubated overnight at 37°C with β-glucuronidase to hydrolyse the conjugated morphine. The total morphine content was then assayed by gas-liquid chromatography using [14C]-morphine to correct for losses during extraction (Fry, Wills & Twycross, 1974). The percentage of administered diamorphine hydrochloride or morphine sulphate recovered as morphine in the urine was calculated taking into account their different molecular weights.

Mean 24 h urinary recovery was determined for each of the three groups. Urinary creatinine was measured by an automated method (Autoanalyser Method N11).

Results

The results from one patient who received diamorphine by mouth were excluded on account of an exceptionally low urine output (122 ml/24 hours). The results from the other patients are summarized in Table 1. There is no significant difference at the 5% level between the mean 24 h creatinine excretion in the three groups, suggesting that the different percentage recoveries were not simply the result of variation in renal function.

In patients receiving diamorphine or morphine by mouth, there is a significant difference at the 5% level in the mean urinary recovery of morphine ($t = 2.1$, d.f. 25, $0.05 > P > 0.01$). On the other hand, no significant difference exists between the mean urinary recovery of morphine in the two diamorphine receiving groups ($t = 0.71$, d.f. 27, $P > 0.4$).

The urinary morphine recovery correlated closely with the dose administered (Fig. 1). Linear correlation coefficients for the three groups were: injected diamorphine, $r = + 0.65$ ($P < 0.05$), oral diamorphine, $r = + 0.94$ ($P < 0.001$), oral morphine, $r = + 0.83$ ($P < 0.01$) and for all the patients $r = + 0.82$ ($P < 0.001$).

Discussion

The mean urinary recoveries in the present study are higher than those reported after single parenteral doses of morphine (Paerregaard, 1957) or after short-term infusions of diamorphine
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Fig. 1 Urinary morphine recovery plotted against administered dose, expressed in terms of equivalence to morphine hydrochloride. (●), oral diamorphine; (○), oral morphine; (△), injected diamorphine.

Differences in analytical techniques might account in part for this but probably more important is the fact that all our subjects had been receiving diamorphine or morphine for some time before the urine collection. In these circumstances, diamorphine, morphine and their biotransformation products will have reached equilibrium throughout the body compartments.

In an earlier report (Fry et al., 1974), we emphasized that there is considerable variation in the urinary excretion of morphine in individual patients from day to day, even when receiving regular steady doses of diamorphine or morphine. Mo & Way (1966) noted similar variation in diamorphine (heroin) addicts receiving repeated known quantities of diamorphine but, despite this, found that the daily group mean urinary excretion of morphine remained virtually constant over 3 days.

Assuming that diamorphine by injection is completely absorbed from the injection site, we postulate that, with our method, a urinary recovery of some 70% represents 100% absorption. This postulate is supported by Mo & Way (1966) who reported a similar recovery (68%) following repeated intravenous administration.

There was no statistical difference between the mean recovery of morphine in those receiving diamorphine hydrochloride by mouth and those receiving it by injection. The recovery following orally administered morphine sulphate was significantly lower. However, the doses of morphine sulphate were, on average, larger than those of diamorphine hydrochloride but there is no evidence of a definite decline in the urinary recovery at the higher dose levels. We conclude, therefore, that an orally administered solution of diamorphine hydrochloride is completely absorbed by the gastro-intestinal tract but that a solution of morphine sulphate is only some two-thirds absorbed.

Many questions remain unanswered: we know nothing, for example, of the rate of absorption of the two preparations or what proportion of the total morphine recovered was previously circulating in a pharmacologically active, non-conjugated form. A more detailed study of serum morphine levels is currently being undertaken to answer these and other questions.
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References


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