BUPRENORPHINE: COMBATTING DRUG ABUSE WITH A UNIQUE OPIOID

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ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION OF BUPRENORPHINE IN ANIMALS AND HUMANS

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INTRODUCTION

This chapter reviews ADME (absorption, distribution, metabolism, and excretion) studies carried out with buprenorphine in animals and humans. The drug was developed in the early 1970s by the pharmaceutical research and development departments of Reckitt & Colman Products, Ltd, UK, leading to its registration in the UK as an analgesic for moderate to severe pain in 1977 (Temgesic Injection® and Temgesic Sublingual® tablets). Since then the products have been registered in over 40 countries. The main findings of ADME studies were summarized in an early review by Heel et al. [1979].

Drug metabolism studies were made difficult because of the high potency of buprenorphine such that at normal therapeutic doses chromatographic techniques were pushed to the limits of sensitivity for measuring plasma and tissue levels of the drug. Much work was carried out to provide a specific and sensitive chemical assay for the drug, with progressive use of gas chromatography (GC), high-performance liquid chromatography (HPLC), and GC/mass spectroscopy. Good, reproducible linear assays have been produced by all three methods, but sensitivity has always been a problem with GC and HPLC and sample throughput is very slow with GC/MS. Parallel development of a radioimmunoassay for buprenorphine gave two antibodies that bind with buprenorphine. Unfortunately, one of the antibodies cross-

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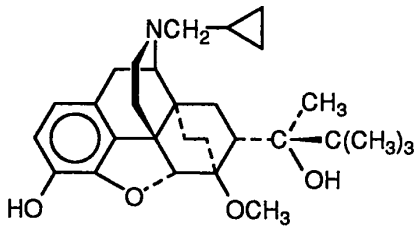
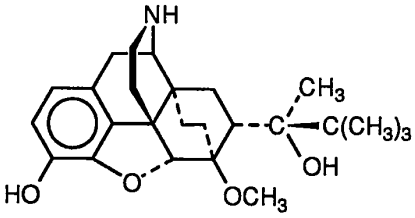


Buprenorphine



N-Dealkylbuprenorphine

Fig. 1. Structures of buprenorphine and N-dealkyl buprenorphine.

reacted with a major metabolite, N-dealkyl buprenorphine (Fig. 1) and the other antibody cross-reacted with the other major metabolite, buprenorphine glucoronide conjugate. However, radioimmunoassay with the first antibody has been used extensively in clinical research and human bioavailability studies because this was the only feasible assay for providing information about the absorption and pharmacokinetics of the drug in humans. Its use in single-dose studies is justified because the contribution of the N-dealkyl metabolite to total immunoreactivity after a single dose is very low; this is discussed later.

Drug metabolism studies are facilitated if a high-specific-activity, stable radiolabeled form of the drug is available. Various options for radiolabeling buprenorphine were considered; the most satisfactory option was a ^{14}C label but the nonavailability of high-specific-activity carbon-labeled precursors and the poor yield in synthetic steps precluded the production of carbon-labeled buprenorphine. Labeling with ^{125}I has been successfully used for the radioimmunoassay [Hand et al., 1986] but this molecule was considered to be too dissimilar to the parent drug for ADME studies.

A method for tritium labeling of buprenorphine to high specific activity was developed using tritium exchange at the 15,16-positions of buprenorphine [Rance et al., 1976]. The suitability of tritium-labeled buprenorphine was assessed by examining lability of the label in rats over a period of 48 hr after a single intramuscular

dose of drug [Brewster et al., 1981a]. Recovery of radioactivity in urine, feces, carcass, and expired air was determined. The lability in each sample was quantified by freeze-drying and distillation to constant specific activity. The total level of lability in the rats ranged from 0.3% to 5.9% of administered dose and the majority of this labile material remained in the carcass after 48 hr, suggesting that it was ^3H_2O. It was concluded from these experiments that the low lability would not be expected to greatly affect the general metabolic picture but could make a significant contribution to total radioactivity in plasma and other tissues when the levels of drug-related material are low, especially at later times after dosing. Therefore, plasma and tissue samples were freeze-dried routinely prior to analysis by combustion.

A comprehensive profile of the metabolism of buprenorphine has been obtained using the tritium-labeled drug in conjunction with chromatographic and radioimmunoassay techniques. This chapter reviews the findings of studies looking first at the results obtained in animals and then examining their similarity to results obtained in humans.

ADME STUDIES IN ANIMALS

Absorption

Most of the studies reported here were carried out with [^{3}H]buprenorphine as part of the drug development program. Another group [Pontani et al., 1985] has also reported ADME studies with the same radiolabel in the rat.

The absorption of buprenorphine has been studied in rat, dog, rhesus monkey [Brewster et al., 1981a; Numata et al., 1981], rabbit, cynomolgus monkey, and baboon [Lloyd-Jones et al., 1980]. Following intramuscular administration of [^{3}H]buprenorphine, blood levels of radioactivity peaked at 10–15 min after dosing in all species (Table I), whereas the absorption peak was delayed following oral (except the rat), sublingual, and buccal administration of the drug. In general, peak blood levels of buprenorphine were higher after intramuscular doses than after larger oral doses owing to extensive first-pass metabolism.

In the rat, *in vivo* studies using *in situ* isolated intestinal loops and portal vein cannulation [Castle et al., 1985] showed that buprenorphine administered into the loop was extensively metabolized to a conjugate by rat intestine, and all the absorbed drug material following a 10-μg bolus, and 90% following a 100-μg bolus, appeared as a glucuronide conjugate [Rance and Shillingford, 1977]. The extensive first-pass metabolism was accompanied by marked enterohepatic cycling of buprenorphine following biliary excretion of conjugated buprenorphine and its probable hydrolysis in the lower gut [Brewster et al., 1981a]. Another study in the rat using the same techniques [Brewster et al., 1981b] presented the absorption profiles (Fig. 2) and the bioavailability (Table II) of buprenorphine following intravenous, intrarectal, intrahepatoportal, sublingual, and intraduodenal administration of 200 μg/kg of [^{3}H]buprenorphine in comparison with the results of intraarterial

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