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**PHARMACOLOGY OF MORPHINE AND THE ACTIVE
METABOLITE MORPHINE 6-GLUCURONIDE:**

**A COMPARISON OF PHARMACOLOGICAL AND
CLINICAL EFFECTS**

being a thesis submitted to the
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for the degree of
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ABSTRACT

Morphine is an effective potent analgesic. However the side effects of nausea, constipation and sedation are seen frequently. Respiratory depression is not such a common problem clinically but is the most potentially dangerous toxicity. An analgesic inducing equivalent analgesic potency without these toxicities would be particularly valuable.

Morphine 6-glucuronide (M6G), one of the major metabolites of morphine, has analgesic activity in animals and animal studies have suggested an improved therapeutic index. The initial study in this thesis confirms the analgesic activity of M6G in man and the pharmacokinetic profile after intravenous and oral administration has been determined. The elimination half life is approximately 1.6 hours with the rate of clearance closely correlating with creatinine clearance. Oral bioavailability at approximately 5%, however, is poor due to its hydrophilic nature.

In an effort to more critically examine the comparative emetic potency of M6G and morphine, both compounds were administered to the ferret, a known emetic model for man. Surprisingly M6G had a greater emetic potency in this model. A pilot pharmacokinetic study performed on the ferret revealed that M6G is only a very minor metabolite accounting for approximately only 1% of the metabolic product of morphine compared to 10% in man. It is possible that other aspects of opiate handling are also different, and reminds us of the importance in studying the drug handling of any

animal model used for the testing of any drug, particularly when metabolites are thought to play a role in clinical effect.

No patients or volunteers in the initial open studies in man experienced any nausea or sedation. This observation prompted a double-blind randomized study comparing the analgesic potency, respiratory depression, nausea and sedation induced by morphine and M6G in normal volunteers. This study confirmed that M6G has an increased analgesic potency in man when compared to morphine and causes significantly less respiratory depression, nausea and sedation.

✓ It has been previously hypothesized that the μ opioid receptor with lower affinity for morphine, the μ_2 receptor, is responsible for the majority of morphine toxic side-effects, including respiratory depression. The last study presented in this thesis utilises radioligand binding studies to determine the opioid receptor binding affinities of morphine and M6G at the μ_1 , μ_2 , total μ and delta opioid receptors. This reveals that M6G has a 5-fold lower binding affinity to the putative μ_2 opioid receptor and hence provides a possible explanation for the decreased toxicity seen compared to morphine.

In light of the findings in man above, further investigation of this active morphine metabolite is therefore indicated as M6G could prove particularly beneficial to those patients with severe underlying pulmonary disease and for obstetric use.

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