



## Mycolactone as Analgesic: Subcutaneous Bioavailability Parameters

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is the bacillus responsible for Buruli ulcer, an infectious disease and the third most important mycobacterial disease worldwide, after tuberculosis and leprosy. infection is a type of panniculitis beginning mostly with a nodule or an oedema, which can progress to large ulcerative lesions. The lesions are caused by mycolactone, the polyketide toxin of . Mycolactone plays a central role for host colonization as it has immunomodulatory and analgesic effects. On one hand, mycolactone induces analgesia by targeting type-2 angiotensin II receptors (ATR), causing cellular hyperpolarization and neuron desensitization. Indeed, a single subcutaneous injection of mycolactone into the mouse footpad induces a long-lasting hypoesthesia up to 48 h. It was suggested that the long-lasting hypoesthesia may result from the persistence of a significant amount of mycolactone locally following its injection, which could be probably due to its slow elimination from tissues. To verify this hypothesis, we investigated the correlation between hypoesthesia and mycolactone bioavailability directly at the tissue level. Various quantities of mycolactone were then injected in mouse tissue and hypoesthesia was recorded with nociception assays over a period of 48 h. The hypoesthesia was maximal 6 h after the injection of 4  $\mu$ g mycolactone. The basal state was reached 48 h after injection, which demonstrated the absence of nerve damage. Surprisingly, mycolactone levels decreased strongly during the first hours with a reduction of 70 and 90% after 4 and 10 h, respectively. Also, mycolactone did not diffuse in neighboring skin tissue and only poorly into the bloodstream upon direct injection. Nevertheless, the remaining amount was sufficient to induce hypoesthesia during 24 h. Our results thus demonstrate that intact mycolactone is rapidly eliminated and that very small amounts of mycolactone are sufficient to induce hypoesthesia. Taken together, our study points out that mycolactone ought to be considered as a promising analgesic.

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