Pharmacokinetics of Methylamines

by

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Abstract

Dimethylamine (DMA) and trimethylamine (TMA) may be nitrosated endogenously to form N-nitrosodimethylamine, which is a potent carcinogen in many animal species. Significant amounts of DMA, TMA, and trimethylamine N-oxide (TMAO) are found in the blood, urine, gastric fluid, and saliva of both rats and humans. Exposure to these amines arises from dietary sources, endogenous synthesis, and synthesis by gut bacteria. A better understanding of the distribution, synthesis, metabolism, and elimination of these methylamines is needed to assess the health risk associated with endogenous nitrosation.

The elimination and disposition of DMA and TMA following an *i.p.* bolus dose was investigated. When 1 μmol of ^{14}C-labeled DMA and TMA was given, 96% of the dose was recovered in the urine in the first 24 hours following the injection. Negligible amounts of radiolabel were recovered in the feces and only a few percent of the dose was found to remain in the tissues after 72 hours. When 100 μmol of ^{14}C-DMA or –TMA was administered, over 90% of the dose was recovered in the urine in 24 hours, but of the same dose of a stable isotope, only 75% of DMA and 56% of TMA doses were recovered in the urine in the same time period. The lower apparent recovery of the stable isotopes may be partially due to larger inherent errors in the analytic method, or a portion of the radiolabel being counted may be in the form of a metabolite. Radioisotope recovery experiments performed in an enclosure with a trapping system found no radioactivity in expired air, either in the form of the methylamine, or as $^{14}CO_2$. From these experiments we conclude that urinary excretion is the primary elimination pathway for methylamines.

There may be a small amount of dimethylamine produced by endogenous pathways (8 μmol/kg/24hr), but much more is produced by bacterial pathways at a rate of 34 μmol/kg/24hr. There is net endogenous metabolism of TMA, so that any bacterial synthesis of TMA which may occur is more than offset by metabolic consumption. In rats with no gut bacteria, there is net metabolism of TMAO by unknown pathways. In normal rats, there is approximately 48 μmol/kg/24hr of TMAO produced by bacterial pathways. This study does not reveal either the precursors involved or the rates of interconversion among the amines, so there may be a substantial amount of TMA produced by bacteria which is subsequently oxidized to TMAO and then either excreted in the urine or metabolized further.

The transient behavior of DMA, TMA, and TMAO in the rat was investigated by implanting a catheter in the jugular vein, administering a bolus dose intravenously, and

taking blood samples at frequent intervals. Three dose levels of 1100 and 1000 μmol were administered. After an initial distribution phase of approximately 30 minutes duration, a one-compartment model was found to provide a good description of the time decay behavior of DMA and TMA over a less than ten-fold range of concentrations. Over a wider range of concentrations, the volumes of distribution and urinary clearances exhibit concentration-dependent behavior. Following a dose of TMAO, we were unable to detect any TMAO in the blood, while significant levels of TMA were found, suggesting that TMAO is very rapidly reduced to TMA in the blood.

Both DMA and TMA have volumes of distribution which are larger than the volume of the animal and decrease with increasing dose. These observations are most likely due to the existence of an active transport system which creates very high concentrations in one or more tissues relative to the blood and is saturable at high methylamine concentrations. The tissue-to-blood concentration ratios at one hour following the dose were measured for heart, lung, liver, kidney, intestine, and abdominal muscle. Several tissues exhibited ratios up to three for both DMA and TMA, while the kidney had a level of DMA eight times that in the blood. Thus, the measured tissue concentrations are qualitatively consistent with the large volumes of distribution for DMA and TMA.

The urinary clearances of both DMA and TMA are higher than the glomerular filtration rate and the clearances also decrease with increasing dose, which suggests that saturable renal tubular secretion occurs. DMA was excreted almost entirely in the urine unchanged. The majority of a dose of TMA is also excreted in the urine, with varying proportions in the forms of TMA and TMAO being dependent on the dose level. TMAO is also excreted almost entirely unchanged in the urine.

The high values and dose-dependence of the volumes of distribution, along with the tissue-to-blood partition ratiois suggest that methylamines are distributed homogeneously throughout the body, but are more concentrated in a few tissues. Although the one-component model appears to fit the experimental data well, it cannot describe these heterogeneities. We have determined the most important sources, sinks, and active tissues of methylamins which will enhance understanding of the potential for *in vivo* formation of nitrosamins and aid in the development of a multi-compartment pharmacokinetic model.

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