Species variations in the *N*-methylation and quaternization of [^{14}C]-pyridine *in vivo*

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It is well known that many phenols, catechols and amines undergo biological methylation *in vivo* and that this reaction is of importance for their activity and disposition. By contrast the *N*-methylation and quaternization of nitrogen functions is much less well understood and explored despite the fact that it was first observed by His in 1887. The biological methylation and quaternization of nitrogen could be of pharmacological interest since the metabolic conversion of tertiary nitrogen to quaternary functions may be expected to be associated with a marked change in both physicochemical and pharmacological properties. Accordingly, we have made a study of the biological methylation *in vivo* in a range of species of the simple heterocycle pyridine as well as with respect to dose and route of administration.

[^{14}C]-Pyridine hydrochloride was administered orally or by intraperitoneal injection to various species including the rat, mouse, guinea pig, rabbit, hamster, gerbil, cat and two human volunteers. The urine was collected for 24 h post-dosing and analyzed for [^{14}C] and *N*-methylpyridinium by reverse isotope dilution. *N*-methylpyridinium excretion was shown to be a valid parameter of its formation since in separate experiments the [^{14}C]-labelled quaternary ammonium compound was shown to be eliminated unchanged in the urine. Table 1 shows the species variations in the urinary excretion of *N*-methylpyridinium following the administration of [^{14}C]-pyridine. The species excreted some 50–75% of the dose of [^{14}C] in the urine within 24 h of administration. There occur however marked variations in the extent of elimination of *N*-methylpyridinium, the product of *N*-methylation, this being low in man, rat and mouse (3–12% dose) and relatively high in the hamster, gerbil, rabbit, guinea pig and cat (20–40% dose).

The *N*-methylation of pyridine in the rat and guinea-pig was independent of route of administration since it occurred when the compound was given both intraperitoneally and orally. In the rat the extent of methylation declined with increase in dose suggesting that this pathway in this species is readily saturable.

The findings show that marked species variations occur with respect to the *N*-methylation and quaternization of pyridine. Similar species differences may exist with respect to the metabolic quaternization of nitrogen heterocycle drugs.

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Table 1 Species Variations in the *N*-methylation and quaternization of [^{14}C]Pyridine *in vivo*

Species	*% dose excreted in 0–24 h urine*	*% dose excreted as N-methylpyridinium*
Man	63	9
Rat	48	5
Mouse	66	12
Rabbit	57	21
Gerbil	52	26
Hamster	67	26
Guinea-pig	66	30
Cat	75	41

Dose of pyridine base was 7 mg/kg given by intraperitoneal injection of an aqueous solution of the hydrochloride except for the two human volunteers where the oral dose was 5 mg. Results are means for 2–5 animals.