Absorption of (−)-nicotine-1′-*N*-oxide in man and its reduction in the gastrointestinal tract

(−)-Nicotine is metabolized to (−)-nicotine-1′-*N*-oxide and (−)-cotinine in man (Bowman, Turnbull & McKennis, 1959; Booth & Boyland, 1970). Nicotine, cotinine and the highly water soluble, but virtually lipid insoluble, nicotine-1′-*N*-oxide* are excreted in urine. Nicotine-1′-*N*-oxide has negligible lipid solubility over the pH range from 2 to 9 (Badgett, Eisner & Walens, 1952) and little absorption from an oral dose would therefore be predicted.

However, oral administration of nicotine-1′-*N*-oxide* results in peak urinary excretion of this *N*-oxide within 2 h of administration (Fig. 1); neither of the two metabolites, nicotine nor cotinine, could be detected until 4·5 h. The amounts recovered as (−)-nicotine-1′-*N*-oxide, (−)-nicotine and (−)-cotinine are shown in Table 1.

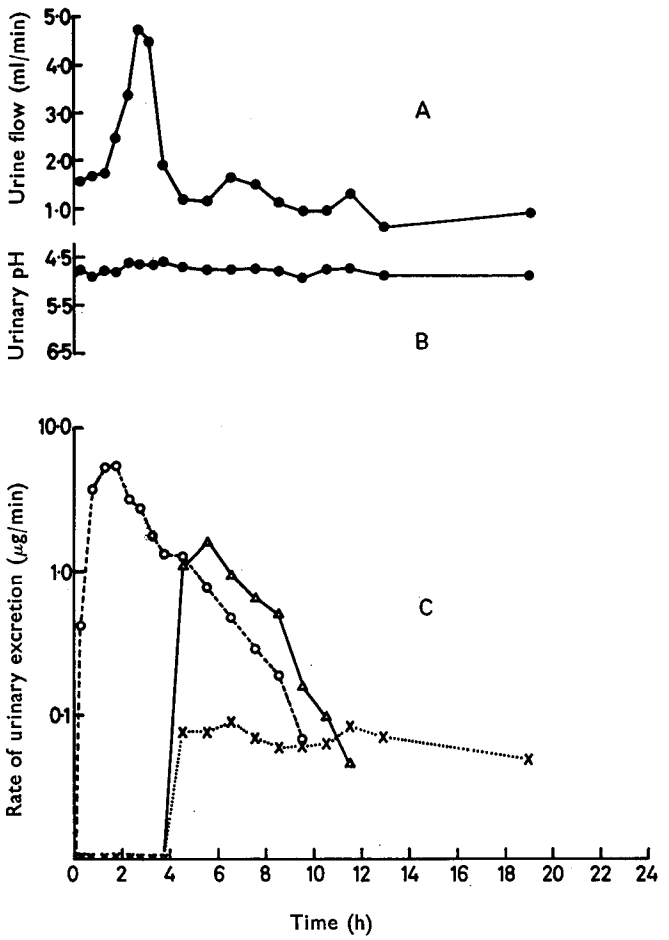

FIG. 1. The urinary excretion of nicotine, cotinine and nicotine-1′-*N*-oxide after oral administration of 2·6 mg nicotine-1′-*N*-oxide under conditions of acidic urinary pH. – – ○ – – Nicotine-1′-*N*-oxide. ——△—— Nicotine. . . X . . Cotinine.

* Mixture of two diastereoisomers.

Table 1. *The urinary recoveries of nicotine-1′-N-oxide, nicotine and cotinine after oral, intravenous and rectal administration of nicotine-1′-N-oxide to subjects with acidic urinary pH (pH 4·8 ± 0·2)*

	% urinary recovery after								
	Oral administration 2·6 mg			Intravenous administration 1 mg			Rectal administration* 2·6 mg		
Subject	*N*-Oxide	Nicotine	Cotinine	*N*-Oxide	Nicotine	Cotinine	*N*-Oxide	Nicotine	Cotinine
1	44·6	15·3	3·4	103	0	0	0·7	8·3	6·3
2	37·7	17·0	3·9	104	0	0	7·0	15·0	7·6
3	29·5	10·5	11·5	—	—	—	—	—	—
4	22·4	15·0	15·0	—	—	—	—	—	—

* Subject 2 was able to retain the solution in the rectum for 5 h but subject 1 for only 1 h.

Approximately twice as much nicotine was recovered in the urine, after oral administration of the *N*-oxide, than when the corresponding dose of nicotine was administered orally. On the other hand, intravenous administration of the *N*-oxide lead to quantitative recovery of this compound in the urine; nicotine and cotinine could not be detected (Table 1).

The results show that circulating levels of nicotine-1′-oxide in the blood are not reduced to nicotine metabolically. The results from oral administration are interpreted by assuming that the highly water soluble *N*-oxide is rendered lipid soluble by ion pair formation under acidic conditions with chloride ions in the stomach. This would account for the rapid peak levels observed in the urine. Some of the material escapes into the duodenum where it is not absorbed due to changes in pH. As the material proceeds down the intestinal tract, reductases in the gut contents or flora, reduce the *N*-oxide to nicotine which is absorbed as such and part of which is then metabolized to cotinine in the liver. Because the nicotine becomes available for absorption further along the gastrointestinal tract than when an oral dose of nicotine itself is given, higher recoveries of nicotine are obtained in the former case since a partial first bypass of the hepatic drug-metabolizing enzymes occurs.

This explanation is supported by the fact that rectal administration of an aqueous solution of nicotine-1′-*N*-oxide results in negligible absorption of the *N*-oxide itself, but the appearance of substantial amounts of nicotine and cotinine in the urine within 0·5 h of administration of the *N*-oxide (Table 1).

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REFERENCES

Badgett, C. O., Eisner, A. & Walens, H. A. (1952). *J. Am. chem. Soc.*, **74**, 4096–4098.
Booth, J. & Boyland, E. (1970). *Biochem. Pharmac.*, **19**, 733–742.
Bowman, E. R., Turnbull, L. B. & McKennis, H. (1959). *J. Pharmac. exp. Ther.*, **127**, 92–95.