N-Oxidation—an important route in the metabolism of methadone in man

Methadone *N*-oxide, as well as methadone and its cyclic metabolite previously reported (Beckett, Taylor & others, 1968), has been found in urine from addicts on methadone treatment and in urine from subjects receiving a single dose of the drug*.

The evidence is as follows. After extraction of the urine under alkaline conditions with n-heptane to remove the parent drug and its cyclic metabolite, subsequent extraction with benzene-chloroform (95:5) followed by t.l.c. (silica; benzene–methanol–diethylamine (75:15:10), Beckett, Mitchard & Shihab, 1971) gave a spot of R_F value 0·4 identical with that of authentic methadone-*N*-oxide. The spot was extracted with benzene-chloroform, the solution evaporated under reduced pressure in a nitrogen atmosphere, at 25° and the product dissolved in buffer (Walpole's acetate buffer pH 5). Cathode ray polarography of the solution gave a reduction peak potential of −1·21 V while reduction with $TiCl_3$/HCl gave methadone (t.l.c. and g.l.c.) and reaction with SO_2 gave a solution from which methadone and its cyclic metabolite (see Beckett & others, 1968) could be extracted, as indicated by g.l.c. and t.l.c. evidence; a solution of authentic methadone-*N*-oxide gave similar results.

Extraction of the above spot, or urine, from which methadone and its cyclic metabolite had been extracted, followed by g.l.c.-mass spectrometry gave a peak whose mass spectra were identical with that of methadone *N*-oxide or 4,4-diphenyl-2-butenylethylketone (prepared from methadone-*N*-oxide by Cope elimination in dimethylsulphoxide and characterized by nmr and accurate mass determination).

Methadone *N*-oxide can be distinguished from possible urinary quaternary ammonium compounds of methadone, e.g. methylquaternary compound (Schaumann; 1960), of similar partition characteristics since the latter undergoes elimination on g.l.c. to give 4,4-diphenylbutenylethylketone as characterized by mass spectrometry. 4,4-Diphenylbutenylethylketone is not separated by g.l.c. from 4,4-diphenyl-2-butenylethylketone even using systems of different characteristics, e.g. 2·5% SE 30 on Chromosorb G: 2 m, 225°, nitrogen (carrier-gas) flow rate 60 ml/min, retention time 3·5 min, and Apiezon L 1%, KOH 1% on Chromosorb G: 1 m, 206°, nitrogen (carrier-gas) flow rate 108 ml/min, retention time 2·3 min.

Results to date show that, in general under normal conditions of urinary pH, the excretion of methadone-*N*-oxide after administration of (±) or (+)-methadone is greater than that of the unchanged drug but less than that of the cyclic metabolite (Beckett & others, 1968; Beckett, 1969).

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