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SHORT COMMUNICATIONS

The quantitive determination and excretion of some phenothiazine type drugs in neuropsychiatric patients*

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NEARLY all the literature on the subject of excretion of phenothiazine-like tranquilizing drugs has dealt primarily with 24-hr urine sampling.[1–3] The quantitative pattern of phenothiazine excretion during smaller time intervals has not been extensively investigated, nor has any attempt been made to assess the relationship between phenothiazine excretion and urine volume. In addition, because it has been shown that to a large extent chlorpromazine is excreted conjugated mainly as the glucuronide,[4] it has been tacitly assumed that glucuronide formation is the primary metabolic path for the excretion of all phenothiazine-like drugs. Investigations, using neuropsychiatric patients, were undertaken to study the excretion of thioridazine in order to study these questions.

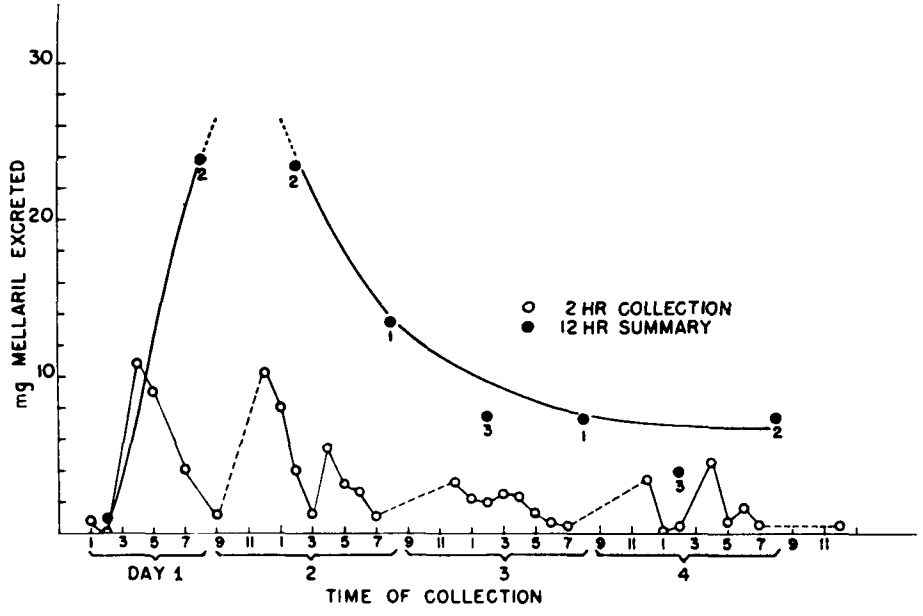

FIG. 1. Excretion curves for single dose of tablet form of drug. The abscissa represents time in terms of 2-hr. collection periods. The dashed portion of the curves indicates where two or more consecutive 2-hr periods are missing. The numbers below each point are the number of specimens missing in that 12-hr period.

The spectrophotometric method employed for the determination of the unconjugated phenothiazine metabolites was that reported previously.[5] Because of the difficulty of accurate sample collection from mentally disturbed patients, investigation of drug excretion based on 24-hr urine collection is subject to

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considerable error. In these experiments we therefore selected a subject with an outdwelling or indwelling catheter and were thereby able to study the rate of thioridazine excretion with reasonable assurance of accurate specimens.

The excretion of thioridazine-like metabolites was found to be most erratic and showed marked fluctuations.* This is illustrated in Fig. 1 for the rate of excretion of drug metabolites after administration of a single 400-mg dose of thioridazine tablets. It should be noted that the excretory peak is reached within the first 24 hr. A comparison with the space-tab (sustained release) form of the drug showed that the peak of excretion was noticeably shifted (after an initial lag period) to about 36 hr after administration of drug. When the drug is administered in either the tablet or space-tab form at a continuing dose of 200 mg b.i.d., marked fluctuations again appeared, with the excretion peak reached at about one week after ingestion of drug (Fig. 2).

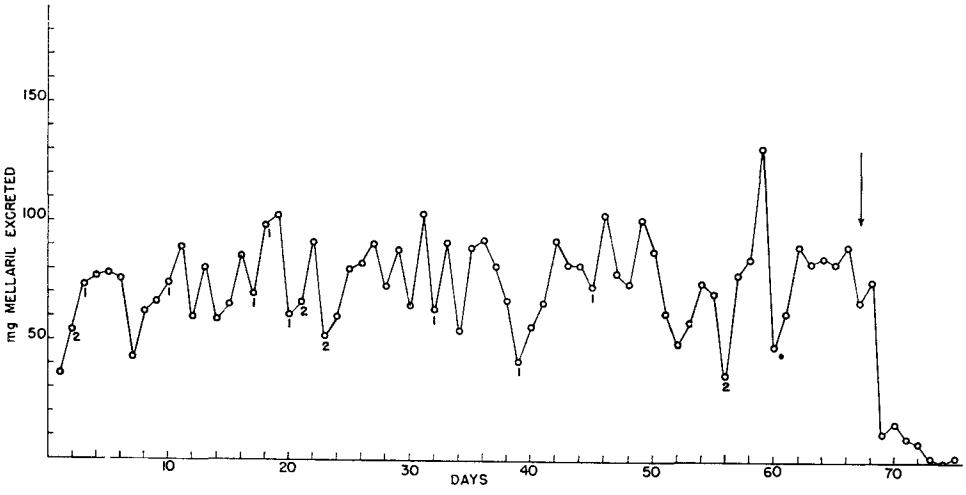

FIG. 2. Continuous dose excretion curve for tablet form of drug. Arrow indicates end of drug administration.

The marked variations and fluctuations of the phenothiazine excreted suggested a relationship between the amount of drug excreted and urine volume.† Such a relationship was demonstrated with the 70-day continuous dose data (shown in Fig. 2), and a correlation coefficient of 0·73 was obtained between drug excretion and urine volume ($N = 250, P < 0{\cdot}001$). When a single dose was administered, the percentage of the total drug excreted at any given time shows a remarkably close correspondence to the cumulative volume per cent (Fig. 3). A similar and close correspondence between drug excreted and urine volume was also seen when thioridazine space-tabs were administered. While the underlying renal mechanism is certainly of obvious interest, further investigation will be necessary before an explanation of this phenomenon is available. It would be interesting to ascertain whether this phenomenon is general for the phenothiazine tranquilizers or is restricted to thioridazine. Our own experience leads us to believe the former.

When chlorpromazine is given to a patient we have observed that a large part of the urinary excretory products may be in the form of the glucuronide. This is suggested by the observation that incubation of urine from a patient given chlorpromazine with β-glucuronidase results in increased color as compared to untreated urine. Lin and co-workers have made similar observations.[4] In our studies of 26 different samples obtained from the same patient taking chlorpromazine over a period of one month, it was found that about 37 per cent of the total urinary excretion was apparently conjugated as the glucuronide. The range was from 15 to 49 per cent. The amounts of chlorpromazine-like

* Chromatography of a chloroform extract of the urinary samples revealed that little or no unchanged drug was being excreted.

† Marked fluctuations still exist if the phenothiazine data are calculated per milligram creatinine.[6]

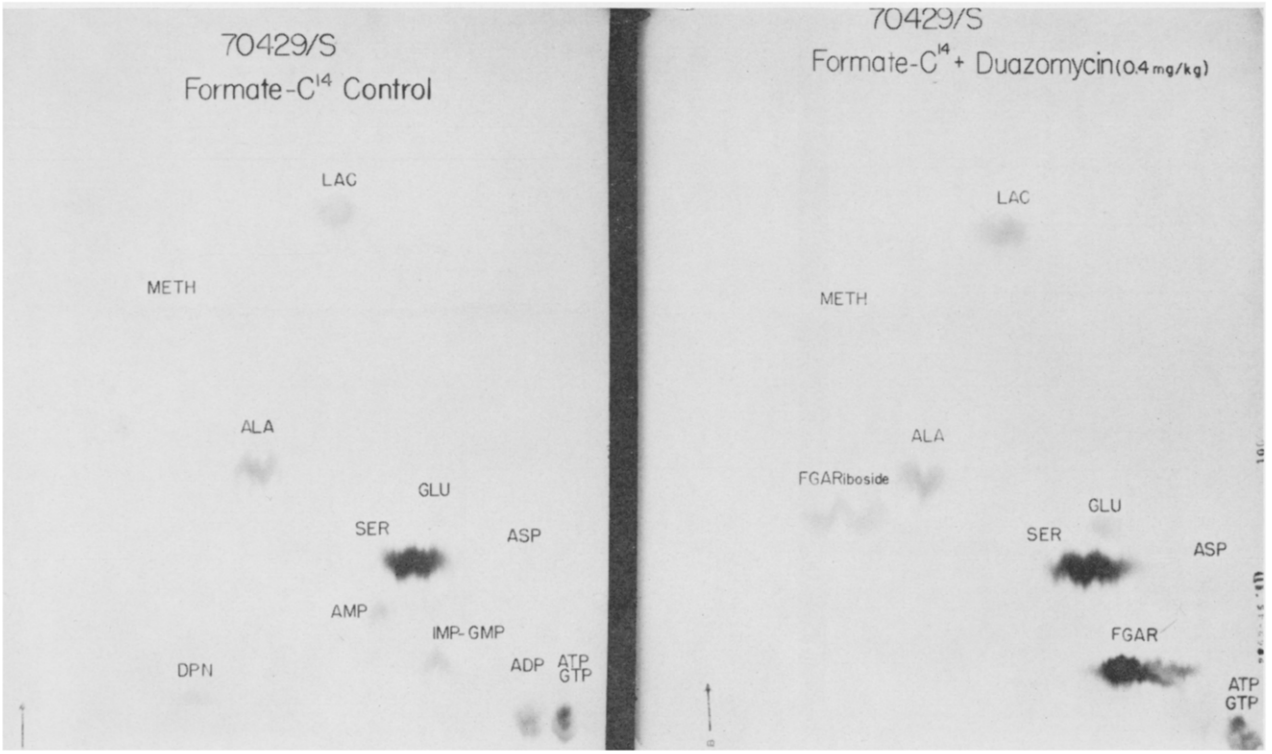

FIG. 1. Effect of duazomycin A on formate-^{14}C incorporation into soluble components of 70429/S cells *in vivo*; radioautograms of two-dimensional chromatograms. Designation of radioactive areas: nucleotides by usual abbreviations, as indicated above; FGAR, formylglycinamide ribonucleotide; FGARiboside, formylglycinamide ribonucleoside; SER, serine; GLU, glutamic acid; ASP, aspartic acid; ALA, alanine; METH, methionine; LAC, lactic acid.

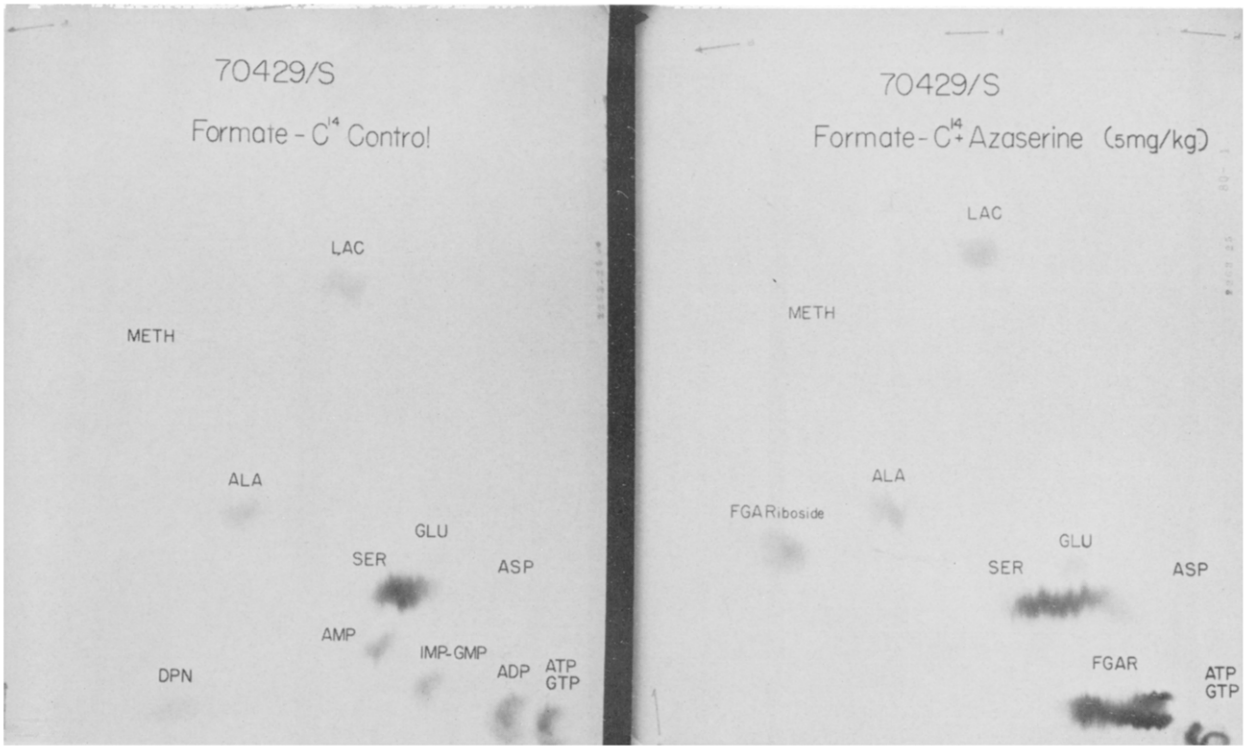

FIG. 2. Radioautograms showing effect of azaserine on formate incorporation into soluble components of 70429/S cells. Designation of radioactive spots as in Fig. 1.

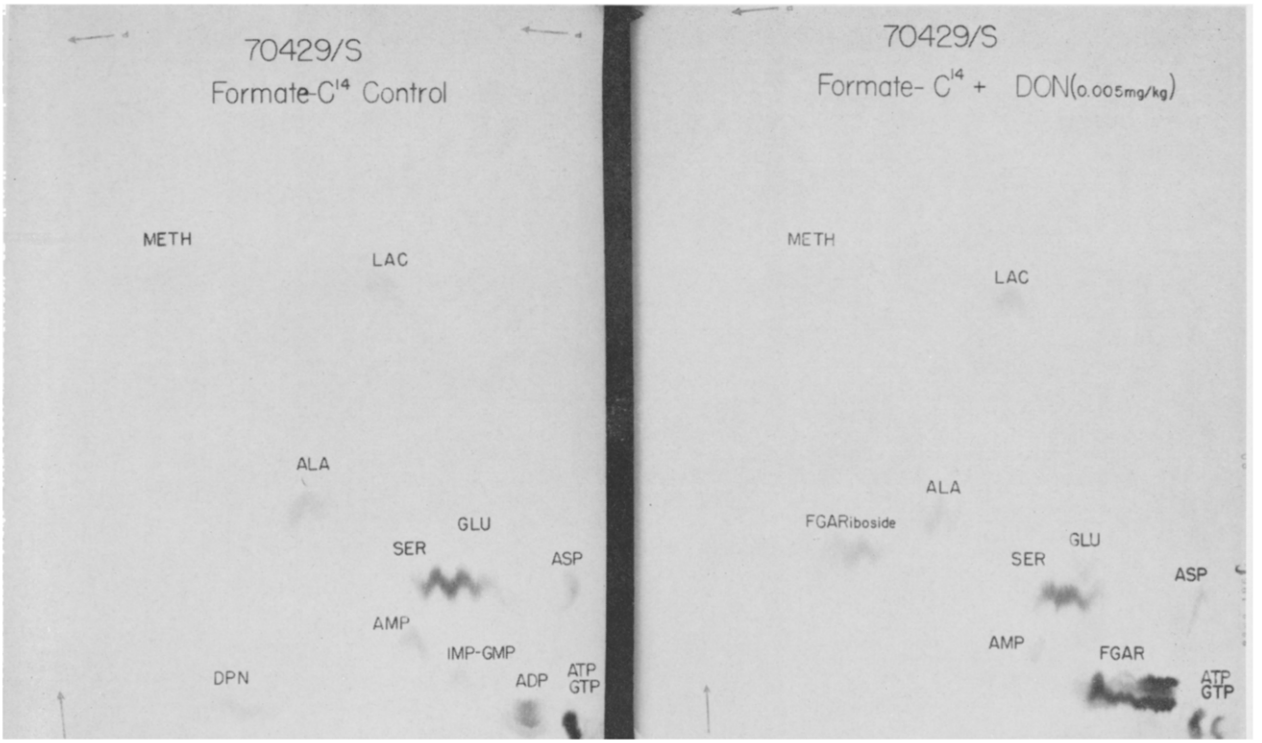

FIG. 3. Radioautograms showing effect of DON on formate incorporation into soluble components of 70429/S cells. Designation of radioactive spots as in Fig. 1.

material ranged in these samples from 20 to 194 mg, and when incubated with the enzyme, the range was 34 to 275 mg. This indicates that the percentage of total drug excreted apparently conjugated as the glucuronide remains essentially the same over a wide range of drug. When thioridazine is the administered drug, however, no glucuronide formation could be inferred because no additional chromogen was obtained after glucuronidase incubation. That thioridazine in the human is not

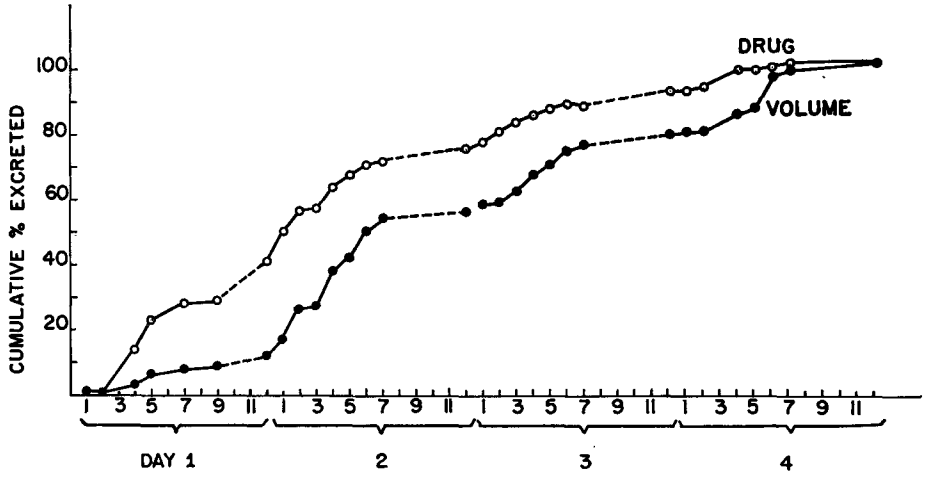

FIG. 3. Cumulative per cent plot—per cent total excretion and per cent total volume.

conjugated to any appreciable extent is supported by our observation that when ^{35}S-ring-labeled thioridazine is administered, less than 3 per cent of the metabolites in the urine are not extractable by chloroform.[6] This is remarkably different from the results obtained with chlorpromazine administration, where over 50 per cent of the urinary metabolites are not extractable with the nonpolar solvent.

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A sensitive and specific assay for the estimation of monoamine oxidase

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MONOAMINE OXIDASE (MAO) activity in tissue is usually measured by manometric[1] or fluorimetric[2] techniques. The former are laborious and require fairly large amounts of tissue; the latter, though more sensitive, still require milligram quantities of tissue and are subject to error because of potential