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# Seven fatal cases involving imipramine in man

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The results of the distribution of imipramine in various organs are reported for four cases of acute overdosage and three cases in which the dose was probably therapeutic. Much lower concentrations of the drug have been found in the blood than in the liver brain and kidney.

ALTHOUGH a number of instances of imipramine poisoning have been recorded (Lancaster & Foster, 1959; Manners, 1960; Somunocuoglu, 1960; Bateman, 1961), reports of the distribution of the drug in the tissues are rare. Denton (1962) describes three cases in which the concentration of the drug in the liver was determined in two (1·9 and 1·25 mg/100 g) but he also showed that the method used for isolation was inefficient. Using a 40% v/v hydrochloric acid digestion for 5 min at 100° and an ultra-violet method of assay he was able to show a recovery of 60–66% of imipramine added to tissue.

There has also been a report of blood levels of 10–60 μg/100 ml in patients receiving 150–300 mg of the drug per day (Gillette, Dingell & Quinn 1960) and Yates, Todrick & Tait (1963), giving 150 mg of the imipramine metabolite, desipramine, to patients, found blood levels of 59–138 μg/100 ml, and also reported an inverse relationship of blood concentration to body weight.

The relation between tissue levels and ingested dose is of great importance to the forensic toxicologist, and the following four cases of fatal poisoning (1–4) and three cases (5–7) in which the dose was most probably at a high (therapeutic) level are reported in an effort to assist in solving such problems.

Cases 1 and 2 were found dead; case 3 had convulsions; case 4 died in coma; case 5 had also taken barbiturates and a phenothiazine in therapeutic dosage and died after about 8 hr in sleep or coma; cases 6 and 7 were found dead, both after being seen alive within 24 hr of death—the postmortem examination showed bronchopneumonia in both. Case 7 was prescribed 100 mg of imipramine per day; the dosage in case 6 was unknown.

Cases 6 and 7 also had monoamine oxidase inhibitors in their possession (Parstelin with phenelzine, and phenelzine respectively). Although deaths from the combination of monoamine oxidase inhibitors and imipramine have been described (Davies, 1960; Babiak, 1961; Luby, 1961) the manufacturer's literature warns against the taking of imipramine within ten days of the cessation of monoamine oxidase therapy.

## Methods

The hydrochloric acid method of isolation has been used. In our hands this gives a recovery of approximately 76% of imipramine added to

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blood. After extraction into ether from alkaline solution, washing and re-extraction into 0·1 N sulphuric acid, the drug has been assayed either by measurement of its ultra-violet spectrum or colorimetrically by Forrests' reagent (Forrest & Forrest, 1960) or by both methods. Full details have been described elsewhere (Curry, 1963).

TABLE 1. DETAILS OF CASES

| Case number | Age | Sex | Estimated weight lb | Time between ingestion and death |
|---|---|---|---|---|
| 1 | 22 | F | 122 | not more than 4 hr. |
| 2 | 46 | M | 140 | found dead after several days |
| 3 | 4 | M | 35 | 3½ hr |
| 4 | 28 | F | 133 | not more than 4¾ hr |
| 5 | 45 | F | 105 | not more than 8 hr |
| 6 | 53 | F | 119 | not more than 6 hr |
| 7 | 55 | F | 77 | not more than 24 hr |

TABLE 2. THE AMOUNT OF IMIPRAMINE IN MG OBTAINED BY ULTRA-VIOLET OR COLORIMETRIC ASSAY

| Case number | Stomach contents | Small intestine contents | Blood | Liver | Kidney | Brain | Bile |
|---|---|---|---|---|---|---|---|
| 1 | 22<br>(20·4) | 17<br>(7·6) | —<br>(0·28) | 22·7<br>(21) | 4·0<br>(3·8) | 3·08<br>(3·0) | |
| 2 | —<br>(18·2) | —<br>— | —<br>(0·57) | —<br>(12) | | | |
| 3 | 240<br>(200) | | 0·6<br>(0·56) | 10·3<br>(8·6) | 6·5<br>(5·6) | 7·2<br>(7·4) | (2·16) |
| 4 | 227<br>(213) | | approx. 1·2<br>(0·7) | (25) | | | |
| 5 | —<br>(2) | | — | —<br>(0·5) | | | |
| 6 | 3·25<br>(1·5) | | (0·033) | 3·2<br>(2·06) | | | |
| 7 | 4·0<br>— | | —<br>— | 4·3, 2·4<br>(1·2) | 1·15<br>(0·5) | | |

The figures in brackets obtained by colorimetric assay.

## Results

Table 1 shows the relevant details of the deaths. Table 2 shows the results of assays on various organs as determined by the ultra-violet and the colorimetric methods of assay.

In case 7 it was found that the concentration in the liver varied with the sampling of the liver. The results are given for two samples. It was then discovered that the drug was firmly bound to the tissue, and the result depended on the proportion of tissue taken to the fluid that had drained from liver into the container.

## Discussion

Neither of the methods of assay will distinguish imipramine from its metabolite desipramine. In the cases of fatal intoxication, correlation of

the colorimetric method and the ultra-violet assay is good, but in the two cases 6 and 7 in which the dose was thought to be therapeutic the ultra-violet method gave significantly higher values. This is probably because of the presence of other metabolites; demethylation and hydroxylation have been found to be involved in imipramine metabolism (Herrmann & Pulver, 1960). It is clear that a consideration of the concentration of the drug in the blood will enable a diagnosis of imipramine intoxication to be made. However, it is not always possible to obtain adequate samples from a decomposed body or from young children, and the interpretation of tissue levels may be necessary. The realisation that liver levels can exceed the blood concentration by a factor of 60 (case 6) will avoid erroneous diagnosis. It may also assist to perform both methods of assay. There is a prima facie reason, supported by this experimental study, that in acute poisoning most of the drug will be in a relatively unchanged condition with a minor proportion of metabolites.

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