Current Practice

Mandrax Poisoning: Conservative Management of 116 Patients

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Mandrax (methaqualone 250 mg., diphenhydramine hydrochloride 25 mg.) poisoning is a common problem. In the first six months of 1966 overdosage with Mandrax accounted for 5% of admissions to the Poisoning Treatment Centre at Edinburgh Royal Infirmary. In the last six months of 1967 this proportion had risen to 10%, so that Mandrax now ranks after barbiturates and salicylates as the drug most often taken in self-poisoning. We believe that a similar pattern obtains elsewhere in Britain, to judge from the increasing frequency of inquiries to the Scottish Poisons Information Bureau regarding Mandrax overdosage, and from the report of an incidence of 15% of self-poisonings in Sunderland being due to Mandrax.[1]

Lawson and Brown[2] recorded the clinical and laboratory findings in the first 29 patients suffering from Mandrax poisoning admitted to this unit, and showed that all recovered when given intensive supportive therapy alone without recourse to methods intended to increase elimination of the drug. Elsewhere forced diuresis is used in the treatment of Mandrax poisoning.[1 3 4] We believe that this is dangerous in a situation where the drug itself can produce pulmonary oedema[5 6] and myocardial damage.[2 7] To demonstrate that intensive supportive therapy is fully adequate and that exposure to the additional risks of forced diuresis is unnecessary, we present the important features and results of treatment of a further 116 patients suffering from Mandrax poisoning.

Patients and Methods

During the 18 months ending 31 December 1967 119 patients were admitted to hospital after having ingested Mandrax. Of these, 46 had also taken other drugs and/or alcohol. Two of these patients have been excluded because it was thought that Mandrax was not the chief cause of their illness. A third patient also is not considered here, as he was very severely poisoned with an exceedingly high plasma level of methaqualone (23 mg./100 ml.). He was treated by intensive supportive measures, peritoneal dialysis, and haemodialysis, and is the subject of a separate publication.[8]

The 116 patients under consideration comprise 68 females and 48 males between the ages of 14 and 76 years. Assessment of the severity of poisoning was based on the levels of consciousness as graded according to Matthew and Lawson.[9] Plasma methaqualone estimations of blood taken on admission were made by the method of Lawson and Brown.[2] Serum aspartate aminotransferase, alanine aminotransferase, D-3-hydroxybutyrate dehydrogenase, and prothrombin time and platelet count were also determined, and the electrocardiogram (E.C.G.) was recorded in most instances. Severely poisoned patients had the E.C.G. and serum enzymes repeated.

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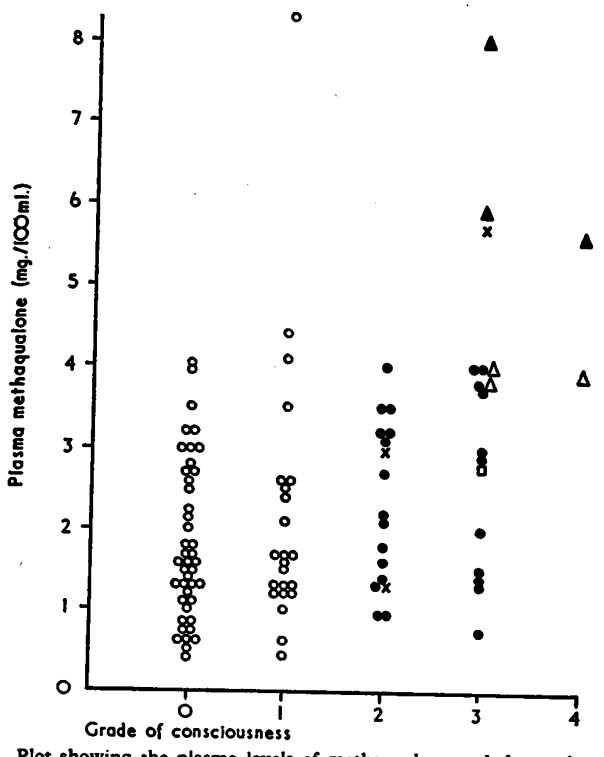
The only treatment undertaken in all patients was the intensive supportive therapy described by Matthew and Lawson.[10] Patients were considered to have regained consciousness when they obeyed simple shouted commands; the duration of coma was measured from the time of admission.

Results

The hypertonia, increased tendon reflexes, and myoclonia recorded by Geldmacher-Mallinckrodt and Lautenbach,[11] Ibe,[7] and Lawson and Brown,[2] were often observed. The plasma levels of methaqualone and the depth and duration of coma for 102 patients are shown in the Chart.

Rises in serum aspartate aminotransferase, alanine aminotransferase, and D-3-hydroxybutyrate dehydrogenase were found in 8 out of 72, 10 out of 76, and 2 out of 25 patients respectively. The platelet count was below 150,000/cu. mm. in 13 out of 65 patients and the prothrombin ratio greater than 1.3 in 9 out of 72. A reversible electrocardiographic abnormality was found in 8 out of 66 patients; the changes were



Plot showing the plasma levels of methaqualone and the grades of consciousness of 102 admissions for Mandrax poisoning. The duration of coma is indicated by the symbols: ○ conscious. ● 0–6 hours. × 7–12 hours. △ 13–18 hours. ▲ 19–24 hours. □ 37–48 hours.

inconstant and included right bundle-branch block, coronary sinus rhythm, and T-wave abnormalities.

All 116 patients survived. Morbidity was low, four patients developing respiratory infection as the only complication. In two of these patients, one of whom required urgent bronchoscopy, there was clear evidence of aspiration of vomitus before admission.

Discussion

The common spectrum of Mandrax poisoning was encountered among the 116 patients. Severe hypotension and respiratory depression, which in poisoning by hypnotic drugs in general are perhaps more important criteria of severity than the depth of coma per se, were not seen.

In the cases presented by Lawson and Brown[2] there was a correlation between the plasma levels of methaqualone and the depth of coma ; a level of 2.5 mg./100 ml. was consistent with dangerous poisoning. Lawson and Brown predicted, however, that the relation of plasma levels to the clinical severity of the poisoning would become less clear-cut as Mandrax became more widely used and particularly as patients became tolerant to it. That tolerance to Mandrax can be acquired is clearly shown by the data in the Chart. Of this series of patients 42 had plasma levels of methaqualone on admission of 2.5 mg./100 ml. or more, but 27 were not severely poisoned, and indeed 20 were conscious. The assessment of severity of poisoning should therefore be made on clinical grounds independently of the results of methaqualone determination. We do not think that the concomitant ingestion of other sedative drugs or of alcohol should influence this assessment.

Abnormal serum enzyme levels, prothrombin ratios, platelet counts, and electrocardiograms were found in a number of patients ; such changes have, however, been noted by previous authors.[2 7 12] The significance of these results is not clear. There does not appear to be close correlation with plasma methaqualone levels.

The management of mild Mandrax poisoning presents no problem. These patients should be kept under careful supervision to sleep off the effects of the drug, as in mild barbiturate overdosage.[9] Lee and Ames,[13] writing with regard to the management of barbiturate poisoning, stated: "All patients . . . who were drowsy or unconscious on reception in the casualty department were immediately treated by forced [alkaline] diuresis." We strongly advise against a similar policy for Mandrax poisoning.

Even in the management of more severe Mandrax poisoning forced diuresis is not indicated on account of the tendency to pulmonary oedema and myocardial damage. Moreover, there is no published scientific evidence showing that forced diuresis enhances clearance of methaqualone or its metabolites. Clinical impressions of the value of this technique in Mandrax poisoning are discouraging. Caridis *et al.*[6] encountered pulmonary oedema and Burston[1] reported no apparent effect even in one patient in whom the procedure was continued for three days.

Peritoneal dialysis and haemodialysis in the very severely poisoned patient will remove little methaqualone at plasma levels below 11 mg./100 ml.[8]

It is fortunate, therefore, that we have been able to show that even in severely poisoned patients intensive supportive therapy alone will ensure a satisfactory outcome without recourse to measures to increase elimination of the drug.

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TODAY'S DRUGS

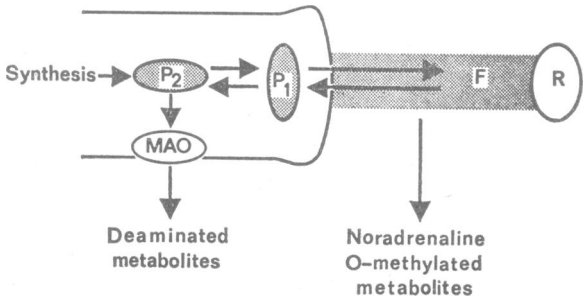
With the help of expert contributors we print in this section notes on drugs in current use. This is the third of a series of articles on drugs in the treatment of depression.

Tricyclic Antidepressants

In the article on the monoamine oxidase inhibitors in Today's Drugs (6 April, p. 35) the importance of noradrenaline (N.A.) and 5-hydroxytryptamine (5H.T.) in normal brain functioning was emphasized, as was the evidence suggesting a deficiency of these amines in the brains of patients with an endogenous (chemical) depression. These amines are stored in an inactive form on binding sites at nerve endings. A deeply bound pool is situated in the region of mitochondria and in proximity to the enzyme monoamine oxidase. A readily available pool is situated close to the receptor site, the two pools being in equilibrium. On nerve stimulation noradrenaline is released from the readily available pool for re-use, only a small proportion being metabolized by the enzyme catechol *o*-methyl transferase to *o*-methylated metabolites (see Fig.). The tricyclic antidepressants act by inhibiting this re-uptake of N.A. (or other amines) on to binding sites, allowing it to act on the receptor for a much longer period. Thus both the monoamine oxidase inhibitors and the tricyclic group of drugs act to increase the concentration of amines at receptor sites, though by different mechanisms.

Clinical Use

It is only ten years since Kuhn[1] published his trial of imipramine (Tofranil) on 500 schizophrenic patients. Unexpectedly he found the drug to have little or no effect on the schizophrenia, but to exert a definite beneficial effect on any associated depressive illness. This emphasizes firstly the importance of observing the side-effects of drugs, and secondly that there is no substitute for the investigation of drugs in the human patient. The tricyclic drugs, unlike the amphetamines,



Simplified model of sympathetic nerve-ending, showing the various monoamine pools.
P_1=readily available pool. R=adrenergic receptor.
P_2=deeply bound pool. M.A.O.=monoamine oxidase.
F=free monoamines.