During saline dialysis in Visking casing folate was rapidly and almost completely dialysed from urine, but a fraction of the serum folate persisted in spite of prolonged dialysis. This suggests that serum folate normally exists as free and protein-bound fractions. Similar initial disappearance rates for urinary and serum folates (Fig. 4) may indicate that urinary folate is unbound and derived from the free plasma folate fraction. The non-dialysable serum folate fraction, which probably represents protein-bound folate, was comparable in normal serum and liver disease, in spite of marked differences in initial total folate levels (see Table). These preliminary results supply no evidence that the folate binder in liver disease differs from that in normal serum. Folate may thus be liberated from the diseased liver in the free form with a variable effect on serum folate levels, depending on the speed with which free folate is cleared by the kidney and the magnitude of folate liberation.

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REFERENCES


Application of Urine Analysis to Diagnosis and Treatment of Heroin Addiction

VINCENT MARKS,* B.M., M.R.C.P.Ed., M.C.Path.; DENYS FRY,† B.SC. P. A. L. CHAPPLE,‡ M.B., CH.B., D.P.M.

GEOFFREY GRAY,§ M.B., B.S.

Summary: Experience with urine analysis for morphine using thin-layer chromatography in 310 cases of real or possible heroin abuse showed that it was valuable not only in detecting improper drug use but also in monitoring treatment. The results of this test can be available routinely in 24, and exceptionally in five hours. A negative result implies that the subject has taken less than 10 mg. of heroin in the past 24 hours.

Introduction

Until 1963 heroin addiction was a relatively minor problem in the U.K. There is still little reliable information on the value of clinical biochemistry in the diagnosis and management of this disorder, though its potential importance has been recognized by the Department of Health and Social Security, which has taken steps to provide laboratory facilities for each of its recently inaugurated drug dependency treatment units.

This paper records experience with urine analysis for heroin (as morphine) in 310 cases of real or possible heroin abuse.

Materials and Methods

Laboratory investigations (Marks, 1966; Marks and Chapple, 1967; Marks and Fry, 1968) were carried out on 310 patients misusing or claiming to be misusing heroin. All had come under the clinical care of one of us (P.A.L.C.) at some time during the four-year period 1964–8, either as an outpatient attending one of several hospitals in the Metropolitan Area or latterly at the National Addiction and Research Institute, Chelsea. Most were seen on at least two occasions, and several upwards of 100 times. Age and sex, as recorded on the first laboratory request form, are shown in the Table. Only those patients (a) from whom urine was collected for analysis on their first consultation for real or alleged drug misuse or (b) from whom at least four urine specimens were analysed during a period of not less than four months, and in whom heroin withdrawal (with or without substitution therapy) was attempted, are considered further in this paper.

None of the patients was (or claimed to be) using heroin alone. Before 1967 most were regularly taking cocaine as well as heroin, and, generally, though more sporadically, other drugs such as amphetamines, barbiturates, and cannabis. During the past year (1967–8) methamphetamine has almost completely replaced cocaine and seemingly is used, at least intermittently, by the majority of heroin abusers.

* Consultant Chemical Pathologist, West Park Hospital, Epsom, Surrey.
† Principal Biochemist, West Park Hospital, Epsom, Surrey.
‡ Medical Director, National Addiction and Research Institute, London S.W.3.
§ Chairman, National Addiction and Research Institute, London S.W.3.
A 50-ml sample of urine was collected in a clean glass container without added preservative and sent to the laboratory for analysis. It was examined in every case for the presence of morphine (heroin is rapidly converted to morphine in the body and is not normally excreted in the urine even after rapid intravenous injection, but is excreted instead as its deacetylated metabolite morphine) and in most cases for the presence of amphetamines and methadone (Physeptone) metabolites, and in some cases for barbiturates and other drugs. This paper is concerned exclusively with the results of morphine assays.

Sex and Age of 310 Patients when First Seen

<table>
<thead>
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<th>Age:</th>
<th>Under 21</th>
<th>21-30</th>
<th>31-</th>
<th>Not Given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>104</td>
<td>70</td>
<td>20</td>
<td>61</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>19</td>
<td>1</td>
<td>12</td>
</tr>
</tbody>
</table>

Urine was examined for morphine qualitatively by thin-layer chromatography. Before 1966 urine was routinely hydrolysed with hot acid (Parker et al., 1966); before separation and identification on thin-layer chromatography, but latterly a modification (Marks and Fry, 1968) of the ion-exchange technique for extracting morphine from urine (Dole et al., 1966) has been used. This technique, though normally detecting only the "free" or unconjugated morphine in the urine, is nevertheless sensitive to a concentration of 1 μg of free morphine per ml, and consequently perfectly adequate for the present purpose, and has the advantage of greater simplicity.

Results and Discussion

New Patients

Urine was obtained from 107 patients who were seen for the first time and claimed to be addicted to ("hooked on") heroin. Urine analysis was positive for morphine in 66, negative for morphine in 37, and in four cases there was insufficient specimen—that is, less than 20 ml.—to permit satisfactory examination. As the results of urine analysis were often not available until more than 72 hours after the patient first appeared at the clinic, immediate treatment was based solely on the "clinical impression" gained by the examining physician (P.A.L.C.) based on the results of the history and physical examination. These are notoriously unreliable diagnostic criteria in patients bent on obtaining heroin either to feed an already established addiction or to start one or in order to sell it.

Of the 37 patients in whom urine was negative for morphine on the first visit, 29 were not prescribed any narcotic drug. Seven of these continued under our care and had further urine analyses. In only one of them was a positive test for morphine ever reported. It is assumed that most of the remaining 22 patients who did not return, and for whom narcotics had not been prescribed, were not addicted to heroin misuse at the time of their first visit, and that their main reason for attending was either to try to obtain a regular supply of heroin—and thereby to change from a "sporadic user" to an established addict—or to obtain heroin to sell.

Eight patients whose urine collected on their first visit was subsequently reported as negative were prescribed narcotics on the basis of clinical impression. Six received methadone and two heroin. We look on these eight patients—and especially the two for whom heroin was prescribed—as "primary" therapeutic failures, as it appears unlikely that any of them were, at the time of their arrival at the clinic, truly addicted to heroin, though they may have indulged in sporadic heroin misuse.

Monitoring of Therapeutic Progress

Data are available on 92 patients undergoing heroin withdrawal or substitution therapy and in whom at least four urine specimens were analysed for morphine during a period of not less than four months. The appearance of morphine in one or more specimens of urine, after a variable period of seemingly satisfactory heroin withdrawal or substitution therapy with negative urine analysis, was referred to as "short-term relapse" when it was followed by further negative urine analyses and as "prolonged relapse" when the latest or, in the case of patients no longer under our care, the last urine to be examined contained morphine. In all cases of "relapse," whether short-term or prolonged, heroin was obtained from another source (or sources) than ourselves.

In 28 patients at least three urine analyses, without interruption, were returned "free of morphine" after the institution of heroin withdrawal or substitution therapy. In 17 patients, on the other hand, urine remained consistently positive for morphine during attempts at heroin withdrawal or substitution therapy. Forty-seven patients with at least three consecutive negative tests for morphine after beginning treatment suffered a relapse; in 15 cases relapse was prolonged and in 32 temporary—on a single occasion in 22 cases, on two occasions in seven, and on three occasions in three.

We have no doubt that the ability to recognize resumption of heroin misuse during substitution (or withdrawal) therapy, before the habit had become firmly re-established, was of great clinical value and enabled us to provide additional psychiatric support at a time when it was most likely still to be acceptable.

Comments

The work summarized in this paper represents mainly the results of investigations undertaken during the past two years largely as a result of experience gained during the preceding three years. We encountered difficulties in organization that we had not previously experienced in clinical investigation of physically ill but psychiatrically normal patients. These seemed to stem largely from deliberate misinformation and unreliability of the drug-dependent patients, who frequently not only refuse to help but often positively obstruct the clinical investigator by failing to keep appointments or to attend for follow up, by failing to provide specimens, and by giving misleading or incorrect answers to questions. Patients not uncommonly take a bottle away with them to pass a urea specimen and return with it empty. Often an excuse is made such as, "I have just passed it, doctor, you should have let me know earlier," but sometimes no explanation is offered, and it is hoped that the omission to provide a specimen will be overlooked. It is common for patients to arrive late at the clinic, and in the ensuing rush the failure to provide a urine specimen may be unnoticed. It is not unknown for a patient to get another to pass a specimen of urine for him—generally in an attempt to produce a false-positive result. Now it is an essential part of our routine not to prescribe any further narcotics until a urine specimen has been obtained.

Despite the difficulties we have experienced in obtaining reliable data certain lessons have been learnt.

(1) Urine analysis is valuable, not only in detecting improper drug use (the main purpose of urine analysis in the United States) but also for monitoring the efficacy of treatment. Ideally urine analysis should be carried out at random at least once a week on all addicts undergoing withdrawal treatment. In our own practice second and subsequent urine specimens were usually collected at the beginning of the week or when there was clinical evidence of relapse. An important point of distinction between heroin addicts in Britain and those in the U.S.A. is that in this country addicts not only claim to be clear of drugs when they are in fact taking them but also may claim to have relapsed when they have not. In our experience this is not uncommon and occurs most often in patients wanting further prescriptions for heroin either to re-establish the habit in themselves or to sell it.
Recently it has been our practice, particularly with younger patients, to use the nalorphine test when it is required urgently to know whether the patient is or is not "hooked on" heroin. A positive test is one in which there is a paradoxical pupil response—that is, one in which the pupils enlarge significantly within half an hour of the injection of 4 mg. of nalorphine subcutaneously. For the purpose of objective measurement, the response is recorded by means of a Polaroid camera, fitted with a pupillometer adapter. Severe reactions to this dose of nalorphine are rare, but should one occur it can readily be relieved by intravenous methadone. Despite the advantage of speed, the nalorphine test is not altogether satisfactory in practice, largely because of its non-specificity and the high incidence of both false-positive and false-negative results.

It is our belief that, provided the work-load justifies the employment of adequate technical and capital resources, the results of a qualitative urine analysis which does not possess the disadvantages of the nalorphine test can be returned to clinicians within 24 hours of receipt of the specimen, and in special cases in as little as five hours.

(2) Possession of objective data by the clinician in place of his complete dependence on the patient's history helps strengthen the doctor-patient relationship. The strength of this bond depends largely on the respect the doctor is able to command from his patient. It is particularly important in the type of patient under discussion, who frequently looks on the doctor as a "dupe" or "square" whose main function is to dispense drugs on demand.

(3) Clinical interpretation of the results of urine analysis may be difficult. Currently there are no methods suitable for detecting morphine in blood routinely; and quantitative measurements of morphine in urine are tedious and for various reasons offer no advantage over qualitative determination (Marks, 1966).

Technically it may not always be possible to identify morphine in the urine when it is present in small amounts. Not only may the quantity present be less than the sensitivity of the method (about 1 μg./ml.), but the presence in the urine of other drugs, or more often their metabolites in high concentration, may serve to obscure what little there is. The phenothiazines and the substitute narcotic methadone are particularly important in this respect. It is largely because these drugs are so often used in the treatment of heroin addiction that we have not found simpler methods of urine analysis for morphine (Harms, 1965; Davidow et al., 1966) satisfactory in our laboratory.

Clinically it is difficult or impossible to distinguish by urine analysis a large dose of heroin administered a long time previously from a small amount taken recently. Nor is it possible to distinguish heroin from morphine. Moreover, absence of morphine from the urine is not conclusive evidence that the subject has not taken heroin; only that, if taken, the dose was too small or too long ago to be detectable. In practice a negative result generally means that less than 10 mg. of heroin has been taken in the past 24 hours. Consequently, a negative result in a patient who does not exhibit abstinence syndrome is good evidence against physical (though not necessary psychic) dependence on the drug. It must be remembered that urine morphine may originate either from heroin or morphine, though currently only the former drug is affected by the recent restriction on prescribing narcotics for addicts. Morphine also occurs in the urine, though only in the bound or conjugated form, of persons taking codeine owing to partial metabolic conversion in the body. This should not give rise to confusion in practice, as codeine is also present in large amounts and is readily detectable on the thin-layer chromatographic plate.

We would like to acknowledge the technical assistance of Mrs. Iris Havard and the helpful collaboration we have received from our many clinical colleagues.

References


Trasicor in Angina Pectoris: a Double-blind Trial


Summary: Eighteen patients entered a double-blind trial of the beta-adrenergic blocking drug Trasicor in the treatment of angina pectoris. Six patients had to be withdrawn from the trial when substitution of placebo for Trasicor caused severe exacerbation of angina attacks. In these cases the frequency and severity of angina attacks fell to a minimum when Trasicor was re-established. A further 10 patients were significantly improved by Trasicor. Two patients showed no significant improvement. No side-effects were observed in doses ranging up to 400 mg. daily.

Introduction

Trasicor is a beta-adrenergic blocking agent which has recently been introduced by Ciba. A haemodynamic investigation of its effects showed that rapid intravenous injection of 5 mg. produced negative chronotropic and negative inotropic effects. In contrast, prolonged oral therapy with Trasicor produced a negative chronotropic and a positive inotropic effect, with a

* Medical Registrar, Napier Hospital, Napier, New Zealand.
† Head Technician, Cardiology Unit, Napier Hospital, New Zealand.
‡ Chief Pharmacist, Hawkes Bay Hospital Board, Napier, New Zealand.
§ Senior Physician, Napier Hospital, New Zealand.