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Lesson of the Week

Methadone maintenance and tuberculosis treatment

Duncan Raistrick, Alistair Hay, Kim Wolff

Drug misusers with tuberculosis who are prescribed rifampicin and methadone may require additional methadone to prevent withdrawal symptoms

Rifampicin is a potent inducer of hepatic microsomal enzymes. It increases drug clearance and reduces the half life of a wide range of drugs, including barbiturates, oral contraceptives, propranolol, sulphonylureas, and methadone.[1] Without a concomitant increase in methadone dose, patients also taking rifampicin are likely to experience opiate withdrawal symptoms and may stop their antituberculosis drugs or supplement their methadone prescription with illicitly obtained opiates. Failure to comply with antituberculosis treatment compromises recovery and increases the risk of secondary resistance.[2] The symptoms of methadone withdrawal usually occur only when intake is reduced and are not expected by a user starting rifampicin. Notifications of tuberculosis in the United Kingdom rose from a plateau of some 5100 in 1987 to over 5700 in 1994. Drug misusers account for only a small number of cases, but they share nationally identified risk factors[3]; thus high rates of tuberculosis can be expected among drug misusers and especially those who are HIV positive.[4]

Case report

A 40 year old woman had first presented for treatment of her opiate dependence at the age of 29. She had experimented with various other drugs, notably amphetamine, since her early 20s. She was judged to have a good prognosis, and after successfully completing an opiate detoxification programme she reported being drug free for four years.

She referred herself back to the clinical service when she was 33 and began a series of methadone maintenance programmes, during which the dose of methadaone was gradually decreased. During this process she stopped using amphetamines and opiates, and her condition was eventually well stabilised with 50 mg methadone daily. When she was 38 a routine chest *x* ray picture suggested tuberculosis and appropriate treatment was recommended.

The antituberculosis drugs induced an opiate withdrawal state, and she responded by stopping taking rifampicin for a month. When the importance of compliance with the antituberculosis treatment was explained, she restarted the treatment and attended the addiction unit to restabilise her condition with methadone. This was achieved by daily attendance at the unit and incremental increases in the dose of methadone until all withdrawal symptoms were suppressed. Ultimately, she required a dose of 150 mg methadone daily (three times her original maintenance dose).

PHARMACOKINETIC STUDIES

The patient participated in four separate kinetic studies at different daily doses; she had been receiving each of the dosing regimens for at least one week—and in one instance (methadone 80 mg), seven months—before these studies were performed. The sequence of the four regimens was: (*a*) methadone 110 mg, rifampicin 120 mg four times a day, isoniazid 50 mg three times a day, pyrazinamide 300 mg three times a

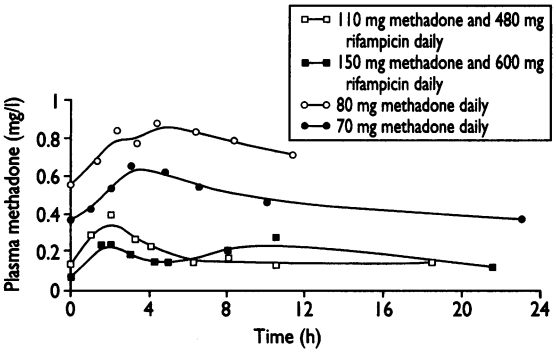

Fig 1—*Plasma methadone concentrations in patient receiving either methadone and antituberculosis treatment or methadone alone*

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day; (*b*) methadone 150 mg (80 mg initially, 70 mg 5½ hours later), rifampicin 150 mg four times a day, isoniazid 100 mg three times a day; (*c*) methadone 80 mg; and (*d*) methadone 70 mg. Plasma methadone concentration was measured by high performance liquid chromatography. Blood was collected before the daily dose (methadone was taken by mouth as a single dose except in the second regimen, when the patient split her dose) and at regular intervals for a further 11 to 23 hours.

Figure 1 shows the results of the kinetic studies. The two lower curves were obtained when the patient was receiving antituberculosis treatment; the two upper curves were obtained 11 and 20 months later, when she was taking methadone alone.

The dose and the time since the last dose of methadone will affect the blood concentration of methadone at baseline before the daily dose is taken. These are likely to be reasons for the difference between the values in the third and fourth regimens.[5] The following pharmacokinetic variables were calculated: oral clearance was 8.97 ml/min/kg for the first regimen, 2.10 ml/min/kg for the third, and 2.12 ml/min/kg for the fourth. We were unable to calculate clearance for the second regimen.

Discussion

So far as we are aware, there are no published reports of an interaction between methadone and isoniazid or pyrazinamide. We assume, therefore, that the lower plasma methadone concentrations during antituberculosis treatment were attributable to the effects of rifampicin. Our methadone measurements agree with those of other clinical reports.[1]

This case shows that some patients receiving maintenance treatment with methadone cannot tolerate withdrawal symptoms precipitated by rifampicin and that they may not comply with antituberculosis treatment until their methadone is increased.

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Caring for Older People

Aids to compliance with medication

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This is the last in a series of 14 articles edited by Eileen Burns, Neil Penn, and Graham Mulley

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Elderly people may need to take several forms of medication, including tablets and capsules, inhalers, insulin, and eye drops. This article describes various aids that are designed to facilitate compliance.

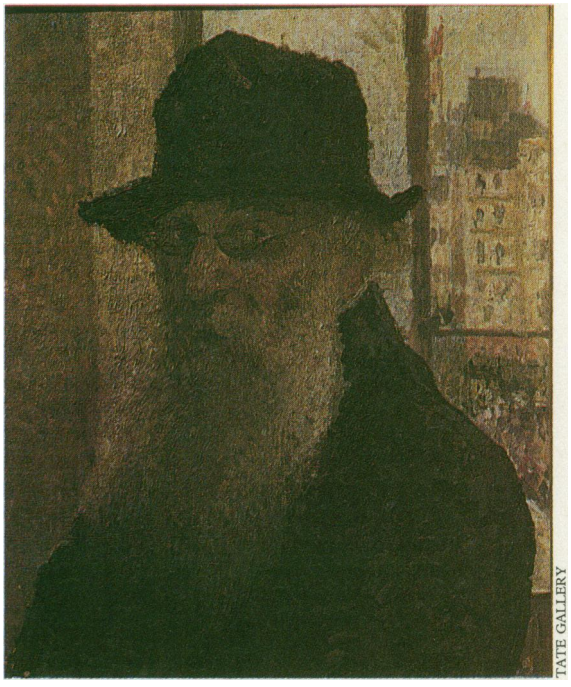
Old people are more likely to suffer from chronic morbidity from multiple diseases—20-30% of older people are taking three or more medications. Several diseases may require concurrent drug treatment; polypharmacy is known to be associated with an increased risk of adverse drug reactions, drug interactions, and poor compliance.

Compliance may be defined as the extent to which a person's behaviour coincides with medical advice. Few patients take their medication as intended by their practitioner; most are partially compliant. Up to 20% of patients do not present their prescription to a pharmacy within one month of issue. Non-compliance is multifactorial and may arise from:

- Not knowing how to take medication (such as orally, twice daily, with food, etc)
- Not understanding the importance of drug treatment in managing disease
- Taking many drugs
- Anticipation or experience of side effects
- Forgetfulness
- Impaired physical function.

Even so, elderly patients with normal cognitive function are more compliant than their younger contemporaries. Simple measures can be taken to improve compliance:

- Educating patients about disease and treatment
- Simplifying drug regimens: minimising the number of drugs and frequency of doses
- Using modified or controlled release preparations to decrease dosage frequency



TATE GALLERY

"Self portrait 1903" by Camille Pissarro (1830-1903)

- Involving carers in management of medication
- Telling patients about common early side effects to which they may develop tolerance
- Using drug diaries, calendars, or medication charts
- Using ordinary bottle tops instead of child resistant containers
- Using large print or jumbo labels on containers
- Using compliance aids, such as dose reminders for tablets and devices to help with administration of inhalers, eye drops, etc.