

Measuring treatment compliance of men with non-gonococcal urethritis receiving oxytetracycline combined with low dose phenobarbitone

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SUMMARY Of 62 men with non-gonococcal urethritis who entered a study to assess compliance with treatment with oxytetracycline, only 33 could be evaluated. Traditional methods (interview and the absence of oxytetracycline in the urine) showed incomplete compliance in nine. Use of low dose phenobarbitone as a pharmacological marker showed incomplete compliance in a further five patients. In addition, phenobarbitone concentrations gave information on the extent to which individual patients had omitted treatment and provided direct, as opposed to circumstantial, evidence of good compliance by most (18) of those studied. Only three of the 33 patients whose compliance was assessed had evidence of continuing infection at follow up, and there was evidence of incomplete compliance in only one of these patients.

Since the time of Hippocrates doctors have been aware that some patients do not take their prescribed medicines.¹ A study of compliance by children with a 10 day course of penicillin found that by the third day 56% had stopped treatment and by the ninth day only 18% were still taking it.²

Measuring compliance is beset by methodological difficulties.³ We have described a new method using low dose phenobarbitone as a measure of compliance.⁴ Phenobarbitone is particularly useful as a marker of compliance because its pharmacokinetics vary relatively little between people and very little in any person. It has a long half life, and ingesting one or two doses before a clinic visit will not achieve plasma concentrations similar to those obtained after treatment for two or more weeks.⁴ Knowledge of the pharmacokinetics of phenobarbitone also allows us to extrapolate backwards from the plasma concentrations in people who claim to have stopped treatment in the past few days and to confirm or refute their stories. The doses used have no discernible sedative effects and do not produce appreciable induction of hepatic drug metabolising enzymes.⁵ In this study we describe the use of oxytetracycline labelled with phenobarbitone to assess the compliance of patients attending a

genitourinary clinic with a diagnosis of non-gonococcal urethritis (NGU).

Patients and methods

Approval for the study was obtained from the Leeds Western Ethics Committee. Sixty two consecutive men, aged 18 to 39, with an initial diagnosis of non-gonococcal urethritis (NGU) (based on five or more polymorphs/high power field in a Gram stained urethral smear) agreed to enter the study. Patients were told that they would receive the standard treatment for their condition, but that the tablets would also contain a small dose of another medicine to allow us to assess whether they had received an adequate dose of their antibiotic. We did not mention "compliance" or "(not) taking tablets". Patients were supplied with bottles of 84 tablets each containing oxytetracycline 250 mg and phenobarbitone 2 mg and were told to take one tablet four times a day. They were asked to return at two weeks, or as soon as possible thereafter, and to continue taking the tablets until they returned. At the return visit patients were asked "Did you take all your tablets?", a urine specimen was taken for oxytetracycline estimation, and 10 ml blood was taken into a lithium heparin tube for measuring the phenobarbitone concentration. Urine was screened for the presence of oxytetracycline as described by Millar and Langdale,⁶ and the plasma phenobarbitone concentration was measured using

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the method of Gill *et al.*⁷ The ratio of plasma concentration to dose of phenobarbitone was calculated for each patient on the basis of his body weight as follows:

$$\frac{\text{Plasma phenobarbitone concentration (mg/l)}}{\text{Phenobarbitone dose (mg)/kg}}$$

Response to treatment was assessed at the return visit by interview, examination, and urethral smear.

Patients who returned on day 14 or earlier were judged to have poor compliance if they had any

evidence (interview, urinary oxytetracycline, or ratio of phenobarbitone plasma concentration to dose) of having omitted tablets. Patients who returned after 14 days were judged to have complied poorly if they showed evidence of not having taken a complete course of treatment for 14 days or evidence that conflicted with a claim to be still taking treatment as instructed.

In addition to the patients, 11 young healthy volunteers taking phenobarbitone (seven taking phenobarbitone alone, four taking oxytetracycline

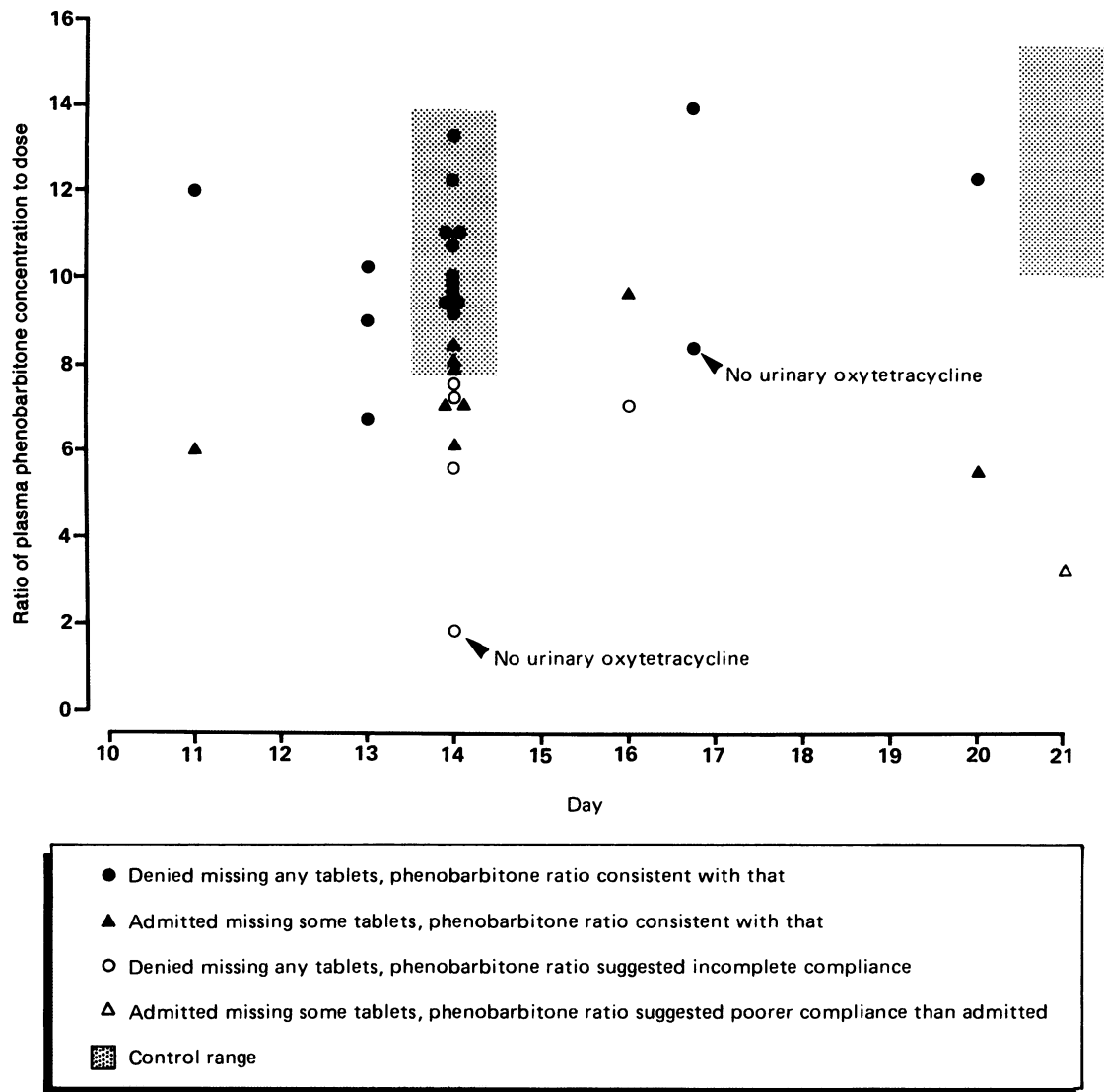


Figure Ratios of plasma concentration to dose of phenobarbitone in 33 men with non-gonococcal urethritis.

and phenobarbitone combined) had their phenobarbitone ratios calculated after 14 days' treatment, and seven of them also had their ratios calculated after 21 days' treatment.

Results

Of 39 patients who returned within 21 days (median 14, range 11–21, days), 33 had plasma phenobarbitone concentrations measured (25 of whom also had urine tested for oxytetracycline) and were assessed for compliance. The remaining six patients returned at a time when neither of the genitourinary doctors in the study was present. The figure shows the results obtained from interview, urinary oxytetracycline, and phenobarbitone ratios.

On questioning, eight patients admitted to stopping treatment one to five days before assessment, though three of them who returned after 14 days claimed to have taken at least 14 days treatment before stopping. A further two patients admitted omitting some tablets in the middle of the course. Of the 25 patients tested, oxytetracycline was absent from the urine of two who both claimed to be still taking treatment, whereas three with detectable oxytetracycline claimed to have stopped taking their tablets at least one day previously (one said one day, two said three days). Thus in nine patients we found evidence of incomplete compliance by traditional methods (interview and testing for urinary oxytetracycline). Eight of these patients were seen on day 14 or later, and four of them had phenobarbitone ratios lower than the range in volunteers at two weeks. In addition, five of the patients who were seen on or after day 14 and showed no traditional evidence of incomplete compliance had phenobarbitone ratios lower than the lowest value for volunteers (at two weeks), and compliance with treatment by these patients was probably also incomplete. One of these patients, who returned on day 21 and claimed to have stopped treatment on the previous day, had a ratio of only 3.3, which certainly showed that he had either stopped treatment much earlier or had taken his tablets inconsistently throughout. On the other hand, seven patients who admitted stopping treatment one to five days before the clinic visit had ratios consistent with their stories. Of the two patients without urinary oxytetracycline, one had a ratio of 1.9 (very low) and the other 8.3 (low). A total of 14 patients with incomplete compliance was thus identified.

Three patients still had evidence of urethritis at their return visit. One of them returned on day 20 claiming to have stopped treatment four days previously, and had a phenobarbitone ratio consistent with this (5.5). Of the other two who claimed to be still taking treatment, one had a ratio of 9.1 on day 13, which was consistent with this claim, but the other had no urinary

oxytetracycline and a ratio of 8.3 on day 17, which suggested incomplete compliance.

Discussion

To our knowledge there have been no reports of tetracyclines altering the pharmacokinetics of barbiturates. The phenobarbitone ratios in our four volunteers who took oxytetracycline combined with phenobarbitone ranged from 7.7 to 11.7, and in two who at other times had taken phenobarbitone alone the ratios were not appreciably altered by the presence of oxytetracycline.

Fewer than two thirds of the patients who entered the study returned for follow up, which is an unfortunate consequence of studying patients with NGU. We cannot tell whether those who failed to return represented satisfied customers who were cured and saw no need to return or people with non-compliant natures who did not bother to return. Of the 33 patients whose compliance was assessed, at least nine had omitted some treatment when assessed by traditional methods. None of these had a high phenobarbitone ratio. Another five, who showed no other evidence of poor compliance, had ratios below the range for healthy volunteers. The phenobarbitone ratios also indicated the extent of poor compliance in men identified by traditional means as being less than fully compliant. Knowledge of phenobarbitone concentrations allowed us to confirm the interview claims of previously good compliance in seven patients who stopped treatment some days before assessment, whereas it provided evidence that compliance was even poorer than stated by a further patient. In addition, 18 patients with no traditional evidence of poor compliance, had a phenobarbitone ratio within the range for healthy volunteers, which suggests that the compliance of those patients was probably good.

The other traditional indicator of compliance, residual tablet counting, was not used in this study. Although it can also give an indication of the extent of tablet taking, it is very open to manipulation by patients, and non-compliant people may "forget" to bring back any tablets.⁴⁸ Furthermore, attempting to arrange for residual tablets to be returned may itself bias the results of a study such as this.

Although evidence of incomplete compliance with instructions for taking oxytetracycline treatment was present in 14 of the patients, the phenobarbitone concentrations indicated that most of them took a substantial proportion of the prescribed course of treatment. Incomplete compliance was a probable cause of treatment failure in only one patient. This may indicate that the prescribed duration (or dose) of treatment with oxytetracycline was more than is required for most cases.

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