Low-dose phenobarbitone as an indicator of compliance with drug therapy

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1 To assess the potential value of low-dose phenobarbitone (PB) as a marker of compliance we studied the relationship between plasma level of PB and dose (2–16 mg daily) following 3 or 4 weeks treatment in healthy volunteers ($n = 26$) and in-patient volunteers ($n = 7$).

2 Also, to simulate poor compliance, PB levels were measured in some volunteers following alternate-day ($n = 6$) or short-term ($n = 5$) treatment with similar doses. These levels, expressed as the level: dose ratios (LDRs), did not overlap with those obtained following 3 or 4 weeks of daily PB intake.

3 To evaluate the efficacy of this marker in patients taking other drugs we gave a group of out-patients ($n = 24$) compound tablets containing B vitamins and a small dose (16 mg) of PB; their compliance over 2–5 weeks was assessed both by measuring plasma levels of PB and residual tablet counting.

4 In the latter study, as well as providing absolute evidence of good compliance by many patients, the plasma levels of PB proved particularly valuable when non-compliant individuals 'forgot' to bring their residual tablets.

5 We suggest that phenobarbitone, in doses low enough to be non-sedative and non-enzyme inducing, is potentially useful as a pharmacological indicator of compliance with drug therapy.

Keywords phenobarbitone compliance drug therapy

Introduction

The great importance of the problem of patient non-compliance is widely recognised (O'Hanrahan & O'Malley, 1981; Eraker *et al.*, 1984; Medication for the Elderly: A Report of the Royal College of Physicians, 1984). About 50% of patients omit some or all of their tablets (O'Hanrahan & O'Malley, 1981; Teeling Smith, 1983; Eraker *et al.*, 1984). The impact of partial compliance on the outcome of treatment will vary with both the drug and the disease in question as well as the extent to which medication is

omitted. Unfortunately, there is no simple way of detecting patients who do not take their treatment as instructed (Pearson, 1982; Eraker *et al.*, 1984; Insull, 1984). Residual tablet counts can be difficult to arrange, do not really prove that drugs have been ingested and are impossible when patients do not return their tablets. Therapeutic drugs, their metabolites, or specially administered marker substances (riboflavin, phenol red) may be measured in patients' blood or urine but, in general, pharmacokinetic differ-

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ences between individuals greatly limit the usefulness of such measurements in the study of compliance (Pearson, 1982; Eraker *et al.*, 1984; Insull, 1984). Furthermore, the presence of a marker which has a short half-life will only indicate compliance at the time of sampling (O'Hanrahan & O'Malley, 1981; Pearson, 1982).

Phenobarbitone (PB) has a half-life of about 4 days in adults. Once age group is taken into account, there appears to be much less inter-individual variation in the relationship of steady-state plasma level to dose with PB than with most other drugs (Svensmark & Buchthal, 1964; Feely *et al.*, 1980). We decided to investigate low-dose PB as an indicator of compliance.

Methods

All studies, in patients and volunteers, were approved by the Leeds Western District Ethics Committee. Plasma concentrations of PB were measured by high-performance liquid chromatography according to the method of Gill *et al.* (1981) with slight modification, using cyclobarbitone 10 mg l^{-1} ($19.6 \text{ } \mu\text{mol l}^{-1}$) as an internal standard. At 1.0 mg l^{-1} the intra-assay and inter-assay coefficients of variation were 3.3% and 4.8% respectively, and the lower limit of detection (signal-to-noise ratio of 3) was 0.05 mg l^{-1} . We plan to publish details of the assay modifications in the near future. Where volunteers were studied more than once at least 6 weeks separated periods of PB administration.

Volunteer studies

Study 1 In an initial study we gave twenty healthy volunteers (14M, 6F; 22-39 years) either PB 15 mg daily ($n = 8$), 7.5 mg daily ($n = 8$) or 7.5 mg on alternate days ($n = 4$) and measured their plasma levels after 3 weeks. Levels were also measured after 1 week in five of the volunteers taking 7.5 mg daily.

Study 2 In a subsequent study, we gave eight volunteers (7M, 1F; 27-40 years), five of whom had been in the initial study, PB 7.5 mg daily for 4 weeks and measured their plasma levels. We then gave them 15 mg daily for a further 4 weeks and measured the levels again.

On another occasion we gave two of these young volunteers (both M), three others of similar age (2M, 1F) and two older volunteers (both F, 57 and 75 years) PB 2 mg daily and measured their levels after 4 weeks. For this latter investigation we used phenobarbitone 2 mg tablets made specially for us at the School of Pharmacy, Manchester.

Study 3 Having obtained their informed consent, we gave six (older) patients (3M, 3F; 65-81 years), in hospital for other reasons, PB 7.5 mg daily ($n = 4$) or 15 mg daily ($n = 2$) and measured their levels after 4 weeks.

Study 4 We gave four young healthy volunteers (all M, 26-39 years) tablets of a compound preparation containing B vitamins and 16 mg of PB (see below) either one daily ($n = 2$) or one approximately every other day, to simulate poor compliance, and measured PB levels after 4 weeks. We also measured levels of plasma PB in two older volunteers, one healthy (M, 51 years) and one an in-patient (F, 76 years), after they had taken the same preparation for 3 and 4 weeks respectively.

The out-patient compliance study

To simulate the inclusion of the marker (PB) in the same tablet as a therapeutic drug we used a compound preparation containing low-dose PB. We chose a preparation containing B vitamins and 16 mg PB per tablet (Beplete, Wyeth). This was one of the compound preparations containing PB which was taken off the market following the action of the Committee on the Review of Medicines on preparations containing phenobarbitone (Drug & Therapeutics Bulletin, 1980). Some stocks were still available and we felt that, in addition to PB, this had the most innocuous constituents of any such compound preparation. Before using it in patients we did a small study in volunteers (see above) to confirm its suitability.

We asked patients attending our general medical follow-up clinic to take one tablet of this preparation daily, in addition to their normal treatment, and to return for blood sampling after a few weeks. For this study we chose, at random, from patients with a variety of illnesses who had brought their medicines to the clinic as part of a study into the accuracy of doctors' records of their patients' current therapy (Price *et al.*, 1986a). We did this to minimise the likelihood that setting up residual tablet counting would make the patients studied aware that their compliance was under scrutiny. We gave them a known supply of both the marker preparation and their therapeutic drugs, and we retained their own tablets and capsules. We told them that the additional tablet contained a small amount of PB. With the agreement of the ethics committee, we told them that the research in which they were being asked to participate concerned methods of judging the efficacy of treatment but, for obvious reasons, we did not mention compliance at this time. At the next

visit they were questioned about their compliance, particularly in respect of the marker preparation, by both the doctor and a pharmacist who subsequently took the residual tablets for counting, and the blood sample was obtained for determination of plasma PB.

Although the available evidence (Perucca *et al.*, 1981) suggested that PB 16 mg daily had little if any effect on hepatic drug metabolism, we excluded from the study patients taking important 'target drugs' for interactions through enzyme induction (e.g. warfarin, oral contraceptives) as well as those taking drugs known to alter PB levels (e.g. valproate).

Results

For every plasma level of PB obtained we also calculated the ratio of plasma level (mg l^{-1}) to dose (mg kg^{-1}). It is this ratio, the LDR, which we use as in index of compliance.

Volunteer studies

In the preliminary study, in twenty volunteers treated for 3 weeks, we found a close correlation ($r = 0.91$, $P < 0.001$) between intake of PB ($\text{mg kg}^{-1} \text{ day}^{-1}$) and plasma level. In this case 7.5 mg on alternate days was taken as 3.75 mg daily.

Figure 1 shows the plasma levels of PB produced by four different doses, each given for 4 weeks to volunteers. This also illustrates the close correlation between level and dose. Because two age groups are included we have not calculated an overall correlation. Taking all the doses used, the LDRs for the younger age group ranged from 9.7 to 14.5 and the LDRs for the older volunteers ranged from 11.9 to 17.4. Among the older volunteers ($n = 10$, 51–81 years) the two lowest LDRs (both < 13) came from two of the three volunteers who were not in-patients.

Figure 2 shows the LDRs after four different regimens of treatment with 7.5 mg daily in young volunteers. The 3 week (daily and alternate day) and 1 week values come from our initial volunteer study and the 1 week values are from five of the eight individuals also studied after 7.5 mg daily for 3 weeks. Neither alternate day treatment for 3 weeks nor daily treatment for 1 week (simulating poor compliance) produced LDRs in the same range as daily treatment for 3 or 4 weeks.

The two young volunteers who took the compound preparation (PB 16 mg) every day had LDRs of 11.0 and 11.2 while the two who omitted it approximately every other day had LDRs of 4.8 and 5.2. The LDRs of the two older volun-

Figure 1 Plasma levels of phenobarbitone produced by 4 weeks treatment with different doses of phenobarbitone. The '16 mg' dose was in the compound preparation containing PB. Conversion factor: Traditional units to SI—plasma phenobarbitone $1 \text{ mg l}^{-1} \approx 4.31 \mu\text{mol l}^{-1}$ ○ 24–40 years, ● 51–81 years.

Figure 2 Phenobarbitone level: dose ratios (LDRs) produced by four different regimens of treatment with 7.5 mg tablets. All subjects were young volunteers (24–40 years). The 1 week data were obtained from five of the eight subjects also studied after 7.5 mg daily for 3 weeks.

teers (one an in-patient) who took this preparation every day were 13.75 and 14.1 and are included in Figure 3.

Only two volunteers, both taking 15 mg day^{-1} , complained of mild sedative effects. Gender, smoking and alcohol intake did not appear to have any substantial effect on PB levels. Intra-individual variation in the LDR was much less among the young volunteers than the inter-individual variation in LDR among this group as a whole. Among the eleven volunteers who took two or more different doses of PB daily for 3 or 4 weeks the lowest LDR was $> 85\%$ of the highest LDR from the same individual in ten (and $> 75\%$ in the 11th).

Figure 3 Phenobarbitone (PB) level: dose ratios (LDRs) compared with the results of residual tablet counting (marker preparation) in the outpatient study. The left hand column shows LDRs from 10 controls (seven in-patient, three volunteers: 51–81 years) who had either PB tablets (2–15 mg), = ●, or the compound tablets with PB 16 mg, = ▲. The other columns show the LDRs from the outpatients grouped according to residual tablet counting of the compound tablets (PB 16 mg). Three younger patients (34–40 years) = △; 21 aged 46–89 years = ▲. (For a detailed explanation see under Results).

The out-patient compliance study

Two otherwise eligible patients were excluded because they were taking drugs excluded by the protocol (warfarin; valproate). Twenty-six patients were asked to participate in the study, one declined and 25 were given known quantities of the marker preparation and their therapeutic drugs. One elderly patient was admitted to hospital during the study and 24 (13M, 11F) returned to the clinic. Three had to be seen after 2 weeks for administrative reasons (holiday Mondays on our clinic days) and all the others were seen after 3–5 weeks. The range of therapeutic drugs being taken by these patients is recorded elsewhere (Price *et al.*, 1986a).

Figure 3 shows the PB LDRs from the 24 patients who returned to the clinic, grouped according to the residual (marker) tablet count. Seventeen patients, all of whom claimed good compliance, returned approximately the correct amount of marker tablets (suggesting they had

taken 90–110% of the correct number). Two patients returned almost all the marker tablets and gave reasons for not having taken them. One of these patients thought they might have been the cause of a heavy nose bleed and the other stopped on the instructions of an ENT consultant who was prescribing betahistine.

Two patients (marked b, in Figure 3) returned an excess of marker tablets, suggesting they had omitted ~ 30%, and three others 'forgot' to bring any residual tablets. All five claimed they had complied well with both therapeutic and marker drug regimens. Thus, residual tablet counting suggested that as regards the marker preparation only two patients had poor compliance but left the three patients who did not return tablets impossible to evaluate. The LDRs for PB showed that two of the latter three (marked c, in Figure 3) were non-compliant and suggested that three others, in addition to the two picked-up by tablet counts, had poor compliance. The only other outpatients with LDRs

< 11 were two (marked a, in Figure 3) of the three who had only had 2 weeks treatment and whose plasma PB was probably not at plateau.

Overall, there was good correlation between the tablet counts for therapeutic drugs and those for the marker but there were some exceptions. The two patients who admitted they had not taken the marker both had good compliance as assessed by counting the therapeutic preparations. Four patients complained of mild sedation while taking the compound preparation containing PB and four others said they felt better while taking it.

Compliance and the control of hypertension

While the outpatients were selected without reference to their disease(s) or response to treatment we have examined the correlation between compliance, as assessed by both methods, and the response to treatment in those patients ($n = 7$) taking treatment for hypertension. Five of them had good compliance by both pill count and the LDR for PB. All five were responding satisfactorily to treatment. Two hypertensives 'forgot' their residual tablets. One was well controlled and had an LDR of 15.5. The other was poorly controlled and during the preceding year had several changes in therapy. No PB was present in his blood and it was later found that he had not even collected his prescription at the pharmacy. At interview, before measurement of plasma PB, the doctor rated his compliance as 'good'. After counselling his blood pressure has been much better controlled than it was during the year before the study.

Discussion

The Workshop on 'Markers for Use as Adherence Measures' (1984) listed dozens of actual or potential markers but did not identify any which have been shown to be really effective. Phenobarbitone (PB) was not mentioned and it was concluded (Insull, 1984) that 'the development of markers and their application in clinical trials was at an early stage'. Our results suggest that PB is a good marker because, among subjects of similar age, the major determinants of steady-state plasma levels appear to be dosage and compliance. While PB, with its long half-life, would be unsuitable for showing whether a drug (e.g. an antibiotic) was being taken every 6 or 8 h, we think that in doses of 7.5 mg (the smallest tablet presently marketed), or less, each day it could have many applications as an indicator of compliance. Previous studies suggest

that no single substance will have pharmacokinetics appropriate to all possible uses of a marker (Insull, 1984).

When we were setting up our out-patient study the available evidence (Perucca *et al.*, 1981) suggested that 15 mg daily produced little, if any, enzyme-induction. We still excluded from the study patients taking important 'target drugs' for interactions through enzyme induction. Our own investigations (Price *et al.*, 1986b) have shown substantial changes in antipyrine clearance in some individuals following doses of 15 mg daily and 30 mg daily but little or no effect with 7.5 mg daily. Also, a few volunteers and patients complained of mild sedation with 15 or 16 mg daily while none of the more than twenty individuals who took 7.5 mg or less complained of sedation. We now use only the latter doses.

Not only did PB provide absolute, as opposed to circumstantial, evidence that many patients took most or all of the tablets but it also allowed compliance to be assessed when patients 'forgot' to bring residual tablets. Although the numbers involved were small, our study suggests that such patients are particularly important. Furthermore, measurement of PB levels appears to have picked up some patients who omitted a substantial number of tablets (? 30–50%) but who were not detected by counting the residual (marker) tablets. The converse was not true, since no patient with a ratio similar to the controls returned more than a few tablets too many.

While asking patients to participate in a research project, and/or setting up the residual pill counts, may have altered compliance in some individuals we believe that the outpatient study still constituted a valid comparison of pill counting and this new method of assessing compliance. We think that the latter proved much superior, although it is by no means perfect.

As a result of our volunteer studies we would expect compliant young adults to have PB levels which give LDRs between 9 and 15 and older people to have ratios between 12 and 17.5 after 3 or more weeks' treatment. LDRs in the upper parts of these ranges suggest very good compliance but those between 9 and 11 in the young and those between 12 and 14 in those aged over 50 years fall in a somewhat 'grey area'. Such patients could be fully compliant but might be omitting up to 35% of their tablets. However, studies in epilepsy (Feely *et al.*, 1980; Takki *et al.*, 1985) and observations in our volunteers suggest that intraindividual variation in the relationship of level to dose is considerably less than interindividual variation. In long-term studies serial measurements might permit the detection of quite modest (> 15%) omissions of treatment,

particularly where an initial measurement was made during supervised administration. While the finding that older people had higher levels is in keeping with observations in epileptics taking PB (Eadie *et al.*, 1977), we are conscious that most of our older 'controls' were in-patients while the younger ones were not. It is possible that imperfect compliance by some healthy volunteers has slightly exaggerated both the difference between young and old and the extent of interindividual variation in both age groups. Adults aged 41–50 years should probably have LDRs very similar to those under 40 years but, to date, we have only studied two volunteers (and three patients) in this age group. We recognise that there is a need for us to better define 'normal ranges' of LDRs for different age groups. For this we will need to study larger numbers of subjects having supervised dosing with PB and we feel that discussion of possible statistical approaches to this aspect is outside the scope of the present paper.

In the outpatient compliance study the blood samples were normally obtained between 2.5 and 5 h after the last dose and we recorded the times at which patients said they had taken the last dose. The samples from our volunteers, including those on alternate day dosing, were drawn between 2 and 12 h after the last dose. We did not try to standardise the time of sampling relative to the last dose since, in the context of these studies, we think that the long half-life of PB makes the time of sampling unimportant. Indeed, we believe that one of the advantages of PB as a marker is that, at steady-state, between-dose fluctuation in plasma concentration is negligible. Nevertheless, in relation to detecting small changes in compliance during long-term studies, we are investigating this further, as part of a current study into the extent of intraindividual variation in steady-state PB levels.

For the compliance study we employed a compound preparation containing PB to simulate the inclusion of low-dose PB in the same tablet or capsule as a therapeutic drug. For some studies, now in progress, we have had tablets containing

PB and a therapeutic drug specially formulated. For other indications, including 'one-off' assessments of individual patients (Feely *et al.*, 1987), we either insert a (tiny) tablet of PB in a capsule of therapeutic drug or incorporate the 'normal' tablet and a PB tablet within one capsule. We believe that using such methods PB could be safely and effectively used in many of the situations where non-compliance is believed to be of major clinical importance. The out-patient study gave an indication of its potential in hypertension and we have also used PB to study compliance in some patients with refractory severe hypertension (Feely *et al.*, 1987). After more than 70 years of widespread use, very few other drugs have been shown to substantially alter PB levels. Also, we have preliminary (unpublished) data which suggest that, notwithstanding a lowering of PB levels by rifampicin, PB could be used to monitor compliance with antituberculous therapy. We believe that this method does not have any significant risks in relation to drug abuse or PB withdrawal phenomena and taken in overdose the total amount of PB we dispense to assess compliance would not cause serious illness. The fact that in the UK, and many other countries, there are already special regulations governing the prescription of PB is both an advantage and an issue which may need to be addressed by regulatory authorities. The availability of an effective indicator of compliance also raises important ethical issues. Nevertheless, we think that it is difficult to overestimate the potential value of PB as a marker. In addition to a usefulness in individual patients with disorders such as refractory hypertension, it could be employed in clinical trials, in assessing other methods of measuring compliance and in evaluating strategies for improving compliance.

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