Br. J. clin. Pharmac. (1990), **30**, 437–441

A comparison of a short half-life marker (low-dose isoniazid), a long half-life pharmacological indicator (low-dose phenobarbitone) and measurements of a controlled release 'therapeutic drug' (metoprolol, Metoros) in reflecting incomplete compliance by volunteers

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1 Although, long half-life compounds appear to be more appropriate pharmacological indicators of compliance with treatment, short half-life markers or measurements of short half-life therapeutic drugs are frequently used.
2 We have compared the usefulness of low-dose phenobarbitone (a long half-life indicator), low dose isoniazid (a short half-life marker) and controlled release metoprolol (Metros) (a controlled release formulation of a short half-life 'therapeutic' drug) in seven volunteers with simulated partial (two thirds) compliance.
3 Detection of isoniazid metabolites in urine had an 83% sensitivity and 94% specificity for detecting ingestion within the previous 24 h and 100% sensitivity and 82% specificity for detecting ingestion within the past 6 h but gave no indication of the longer term pattern of compliance.
4 At 28 days (a time when steady-state would be obtained for all three drugs) phenobarbitone plasma levels were 70% (66–76%)—median and interquartile range—of the expected steady-state level if compliance had been complete. Corresponding figures for metoprolol were 82% (37–100%).
5 Measurement of phenobarbitone was much superior to isoniazid or metoprolol measurements in reflecting partial compliance over the previous 1 to 4 weeks.

Keywords compliance phenobarbitone isoniazid metoprolol

Introduction

It is widely accepted that poor compliance with prescribed treatment is an important cause of inadequate response to treatment (Eraker *et al.*, 1984; Lasagna, 1973). Of the available methods of measuring compliance it is now apparent that patient interview and return tablet/container count are misleading and virtually useless (Pullar *et al.*, 1989; Rudd *et al.*, 1989). Of the remaining techniques, measurement of drug level and electronic monitoring of removal of drug from the container, only the former confirms tablet ingestion.

Measurement of drug level can utilise the therapeutic drug or a pharmacological indicator (quantitative) or marker (qualitative). For many years one of the stated requirements of a phar-

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macological marker/indicator has been that it is non-cumulative (i.e. has a short half-life relative to the dosing interval) (Gordis, 1984; Insull, 1984; Pearson, 1982; Porter, 1969). One consequence of this 'requirement' is that measurement of the drug will only give information regarding ingestion of the previous one or two doses. More recently, it has been suggested that a long half-life (cumulative) indicator provides appropriate measurement of compliance as this will be much less sensitive to the effect of the last one or two doses and gives an indication of compliance over the previous few weeks (Feely *et al.*, 1987; Manenpaa *et al.*, 1987). Such indicators have been used in a number of recent studies of compliance.

The measurement of therapeutic drug levels has at times been used as a 'gold standard' (Anon., 1990) but although it may possess a superficial attractiveness, its value is dependent upon the pharmacokinetic considerations discussed above. In addition, particular therapeutic drugs may demonstrate a large degree of inter-individual variation in pharmacokinetics and each drug studied will require a separate assay and definition of an 'expected range'. In this study we have compared the usefulness of the information on compliance obtained from the measurement of a short half-life pharmacological marker (isoniazid) (Ellard *et al.*, 1980), a long half-life pharmacological indicator (phenobarbitone), and a 'therapeutic drug' (slow release metoprolol, Metoros), in healthy volunteers with simulated poor compliance. The latter was chosen as the 'therapeutic' drug as it appeared to have little inter or intra-individual variation in its steady-state plasma concentrations over a 24 h period (Good *et al.*, 1985). In addition to comparing the information gained from each method a secondary aim was to examine whether the combination of a long-term indicator and short-term marker gave additional useful information.

Methods

Approval for the study was obtained from the Leeds Western District Research Ethics Committee. Seven healthy volunteers (age 28–43 years; 5 M, 2 F) were studied. Volunteers were given oral isoniazid 6 mg, phenobarbitone 2 mg and sustained release metoprolol 190 mg daily on 2 days out of 3 (missing day 2 and every 3rd day thereafter) for 28 days and subsequently daily for another 2 days. On weekdays ingestion was supervised and at weekends each subject was telephoned at home and asked to take their tablet during the telephone call. The ingestion of tablets on days 29 and 30 were to allow the volunteer to achieve steady-state for metoprolol and isoniazid. All the volunteers had previously been given a supervised 28 day course of phenobarbitone 2 mg daily in order to define their steady-state levels with full dosing.

During the simulated poor-compliance study, venous blood was taken for measurement of plasma phenobarbitone and metoprolol on days 0, 8, 15, 22, 28, 30 and 32 immediately before and 2 and 6 h after the time of dosing. At each of these times a urine sample was also taken for detection of isoniazid. Plasma metoprolol was assayed by gas liquid chromatography (Good *et al.*, 1985). The lower limit of detection for the assay was 5 ng ml^{-1}, the CV of the assay for a standard of 11.7 ng ml^{-1} was 4.6%. Phenobarbitone was assayed by h.p.l.c. (Peaker *et al.*, 1989), the lower limit of detection being 50 ng ml^{-1} and the CV was 9% for a 50 ng ml^{-1} standard and 2.9% for a 500 ng ml^{-1} standard. Isoniazid metabolites, isonicotinic acid and isonicotinyglycine, were detected in the urine using a colorimetric technique (Ellard & Greenfield, 1977). Reacted samples were read blindly by two observers who consistently agreed with each other. The observers were able to detect concentrations above 2.0 μg ml^{-1}. Metoprolol and phenobarbitone concentrations were expressed as a percentage of that measured in a sample taken with the same time relationship to dosing at steady-state. Phenobarbitone concentrations from days 8, 15, and 22 were also expressed as a percentage of the concentration measured at the respective time and day during the build up to steady state concentrations during the control study.

Results

Table 1 shows the 28 day results for phenobarbitone and metoprolol during simulated poor compliance (tablets taken days 27 and 28), expressed as a percentage of the respective value found at steady state. It also shows whether or not isoniazid metabolites were detectable in urine. With simulated partial (67%) compliance the median phenobarbitone level expressed as a percentage of the steady-state concentration was 70% (interquartile range 66–76%). On the other hand, the median metoprolol level expressed in the same way was 82% (interquartile range 37–110%). Despite tablets having been taken on days 27 and 28, 3 of 21 'day 28' urine samples were negative for isoniazid metabolites. All three negative urine samples were collected at time 0 (i.e. 24 h following the previous dose).

Table 2 shows the phenobarbitone and meto-

Table 1 Phenobarbitone and metoprolol plasma levels on day 28 of simulated poor compliance expressed as a percentage of the respective steady-state concentration. Isoniazid metabolites are shown as detectable (+) or undetectable (−)

	Phenobarbitone			*Metoprolol*			*Isoniazid*		
Time	*0 h*	*2 h*	*6 h*	*0 h*	*2 h*	*6 h*	*0 h*	*2 h*	*6 h*
Volunteer									
1	58%	77%	70%	0%	24%	61%	−	+	+
2	80%	91%	84%	80%	100%	93%	−	+	+
3	82%	76%	74%	60%	29%	82%	+	+	+
4	66%	70%	65%	0%	0%	50%	+	+	+
5	65%	73%	66%	136%	100%	116%	+	+	+
6	60%	66%	66%	100%	100%	60%	+	+	+
7	69%	73%	77%	214%	200%	104%	−	+	+

Table 2 Phenobarbitone and metoprolol levels during simulated poor compliance expressed as a percentage of 'control' values (medians and ranges). Number of urine samples positive for isoniazid metabolites

Day	*Time (h)*	*Phenobarbitone (%)*	*Metoprolol (%)*	*Isoniazid (number of positive results)* n = 7
8	0	89 (82–100)	105 (67–143)	3
	2	*	41 (UD–100)	1
	6	67 (54–76)	UD (UD–42)	2
15	0	60 (54–72)	UD (all UD)	0
	2	*	UD (UD–22)	7
	6	73 (67–86)	77 (36–114)	7
22	0	71 (63–83)	82 (UD–105)	1
	2	*	68 (UD–214)	7
	6	73 (69–79)	104 (50–143)	7
30	0	86 (69–96)	**	2
	2	89 (81–95)	**	7
	6	85 (71–90)	**	7
32	0	71 (61–88)	UD (all UD)	0
	2	59 (54–74)	UD (all UD)	0
	6	56 (52–76)	UD (all UD)	0

UD – undetectable
* – 'control' values not available
** – these day 30 values were used as 'control' steady-state levels for metoprolol

prolol levels expressed as a percentage of the appropriate control values (median; range) and the number of samples with detectable isoniazid from days 8, 15, 22, 30, and 32. On day 1, isoniazid metabolites were absent from all time 0 and present in all 2 h and 6 h in all samples.

Over the whole study the sensitivity and specificity of the test for urinary isoniazid metabolites for detecting ingestion of tablets within the past 24 h was 83% and 94% respectively. However, for detecting ingestion within the previous 6 h these figures became 100% and 82% respectively.

Discussion

Previous work has shown that by far the commonest situation is not 'compliance' or 'non-compliance' but 'partial compliance' where patients take most of their tablets most of the time (Cramer *et al.*, 1989; Pullar *et al.*, 1988a). Since there is no 'gold standard' with which to assess partial compliance in patients, it was necessary that this comparative study was carried out in volunteers with a known pattern of partial compliance. The results show clearly that in this particular situation of 'regular' poor compliance

low dose phenobarbitone was the best indicator of overall compliance. In addition, on day 30, when volunteers had taken tablets daily for the last 4 days, phenobarbitone levels were all less than the expected steady-state levels. This indicates that it remains a sensitive measure of compliance even when compliance has been improved for the few days before sampling, a likely clinical event—the so-called 'toothbrush' effect. In contrast, the 'therapeutic' drug which we chose for this experiment, sustained release metoprolol, was unable to give an indication of the overall pattern of compliance. This is not surprising as it has a short half-life. However, its controlled release characteristics, which result in sustained levels over a 24 h period followed by a rapid fall off in levels (Good *et al.*, 1985), should make it an ideal measure of compliance with the immediately previous dose. This was not the case and this appears to be due to a marked intra-individual variation in levels.

In this experiment both phenobarbitone and metoprolol levels were compared with the steady state levels in the same individual. This is occasionally (De Souza *et al.*, 1988), though by no means always, possible in studies of patient compliance. Thus, because of the need to resort to an 'expected range' for steady-state levels, results in most patient studies using low dose phenobarbitone will give a somewhat less accurate measure of overall compliance for an individual, though they will give an accurate estimate of the level of compliance within the population (Pullar *et al.*, 1989). Despite this criticism, low-dose phenobarbitone is still a very useful indicator for identifying poor compliance in individuals and, although its specificity is greater than its sensitivity, it is much more sensitive than the traditional measure of compliance (Pullar *et al.*, 1988a, 1989). Its usefulness in assessing compliance in individuals may be enhanced further with the use of a pharmacokinetic model to predict expected steady-state concentrations (Feely *et al.*, 1989; Kumar *et al.*, 1989a). In addition the doses of phenobarbitone used do not appear to be associated with enzyme induction (Price *et al.*, 1986), psychomotor impairment (Kumar *et al.*, 1989b) or adverse symptoms (Pullar *et al.*, 1988b). Despite claims that the ideal pharmacological indicator of compliance has a short $t_{1/2}$ (Gordis, 1984; Insull, 1984; Pearson, 1982; Porter, 1969), we would not have expected low-dose isoniazid to give an indication of compliance over a period any longer than the previous 18 h and even in higher dose (13 mg) would only be useful over the previous 24 h (Ellard *et al.*, 1980). We found the 6 mg dose to be very sensitive for identifying ingestion over the last 6 h but on 18% of occasions when ingestion was longer than 6 h previously it gave a false positive result. It was much more specific for identifying compliance within the previous 24 h but failed to detect such ingestion in 17% of cases. As can be seen from the 2 h and 6 h results on day 1 it gives no indication of the pattern of ingestion prior to the last dose. Again, the doses of isoniazid used are not known to have any hepatotoxic potential.

We conclude that, as expected from its kinetic characteristics (Feely *et al.*, 1987), though not necessarily from the literature (Gordis, 1984; Insull, 1984; Pearson, 1982; Porter, 1969) low-dose phenobarbitone gave the most useful information on compliance in this study. Although isoniazid gave accurate information on ingestion over the previous 24 h this information is of limited clinical usefulness. The concurrent use of a short half-life (short-term) marker e.g. isoniazid and a long half-life (long-term) indicator e.g. phenobarbitone might be expected to give a more accurate picture of the overall pattern of compliance than either alone. However, in this study isoniazid added little to the usefulness of low-dose phenobarbitone. It may be that the best measure of compliance would be a combination of a long half-life indicator which confirms ingestion, with an electronic monitoring system which records the timing of removal of tablets from the container.

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(Received 27 February 1990, accepted 22 May 1990)