revealed no survivors after 20 min at 121 °C in several instances growth of survivors did not become evident until several days incubation had elapsed.

The standards of heat resistance claimed by four of the manufacturers are those recommended by the United States Pharmacopeia (U.S.P.) XIX for biological indicators. viz. all items having survivors after 5 min but none after 15 min exposure at 121 °C. The fifth manufacturer follows the recommendations of Kelsey (1961), i.e. 50% with survivors after 5 min and none after 10 min at 121 °C.

The results in Table 2 show that preparations A and E approach the U.S.P. specification but only F strictly conforms to it. All three, however, may be considered satisfactory in view of the sampling errors associated with low levels of survivors. An acceptable performance by three out of six preparations represents a slight improvement in reproducibility over that observed by Meyernik (1972), but it is clear that some spore preparations are still available which do not meet their own label claims, or alternatively, the U.S.P. specification, and thus cannot give adequate assurance of satisfactory sterilization.

Table 2. Number of test items* showing survivors after exposure to 121 °C for different times.

Exposure time min	Preparation A	B	C	D	E	F
5	20	0	20	4	19	20
7	20	0	20	0	16	20
9	20	1	20	0	16	20
11	10	0	20	0	0	18
13	2	0	16	0	1	0
15	2	0	14	0	0	0

* Out of a maximum of 20.

The problems associated with poor reproducibility of biological indicators are widely recognized and have led to a reluctance on the part of official bodies in Britain to support their widespread use (Rosenheim 1973; Guide to Good Manufacturing Practice 1977). Attempts to produce *B. stearothermophilus* spore suspensions of predictable and uniform heat resistance by growth and sporulation in both chemically defined (Lee & Brown 1975; Friesen & Anderson 1974) and complex media (Heinz et al 1976) have been reported. The results described here suggest that there is ample scope for further work to be conducted with these objectives in mind.

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Amitriptyline pharmacokinetics. Lentizol and ordinary amitriptyline tablets compared in a cross-over study of steady state plasma drug levels in depressed patients

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Lentizol, a sustained-release form of amitriptyline, was compared with ordinary tablets of the drug (Saroten) in a cross-over study of single doses in healthy subjects (Burch & Hullin 1981) the preparations being supplied by W. R. Warner (Pontypool, U.K.). Six depressed patients have now been treated with each of the formulations in turn and plasma drug levels in the steady state have been compared. Doses of 50 or 100 mg were given once daily, at 9 a.m. or 9 p.m. To avoid patients giving blood samples at frequent intervals during two days (or nights), neither the times of peak plasma drug levels, nor the heights of the peaks were measured. However, any slowing of the absorption of amitriptyline from the gut should result in higher plasma levels of the drug late in the interval between doses, provided that bioavailability is not reduced.

After 10 or more days administration of a constant daily dose, plasma levels of amitriptyline and of nortriptyline 12 h and 24 h after the dose were determined on several days for each patient on each formulation (Table 1).

Blood samples were treated and plasma concentrations of amitriptyline and nortriptyline were determined as described by Burch et al (1979). Values obtained on

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Table 1. Ratios of mean plasma drug levels produced by sustained release product (L)/ordinary tablet (S). (AT) amitriptyline (NT) nortriptyline.

Patient		I	II	III	IV	V	VI (1)[a]	VI (2)[a]	VI (3)[a]	Mean
Sex		F	M	F	F	F	F			
Age		22	39	65	69	70	47			
AT dose (mg):										
1st period		50S	100S	100S	100S	100L	100S	50S	100L	
2nd period		50L	100L	100L	100L	100S	100L	50L	100S	
Time given		9 pm	9 pm	9 am	9 am	9 am	9 am	9 pm	9 pm	
Drug level ratio:										
12 h after dose	AT	1·16	0·92	1·02	1·14	0·88	0·72	0·90	1·36	1·01
	NT	1·00	1·07	1·06	0·83	0·81	0·87	0·85	1·62	1·01
24 h after dose	AT	1·02	1·21	1·18	1·25	1·10	0·66	0·93	1·40	1·09
	NT	1·01	1·15	1·04	0·81	1·00	0·79	0·88	1·75	1·05

[a] Patient VI was studied 3 times, with an interval of 8 months between studies (1) and (2). Study (3) followed study (2) immediately.

Other drugs were given, in constant doses at fixed times throughout the study period, as follows: lithium carbonate to patients III and VI, nitrazepam to patients IV and V, flurazepam to patient II and an oral contraceptive to patient I.

successive days indicated that steady states had been attained. The ordinary tablet was usually, but not always, given before the sustained release product; however, neither the results of the present study, nor weekly measurements of plasma amitriptyline and nortriptyline during a clinical trial suggest a rise or fall on average, once the steady state has been reached (Burch unpublished observations).

Table 1 gives particulars for each patient and summarizes the results by comparing the mean plasma drug level found for the two preparations, in the same subject at the same time of day.

Twenty-four hours after the dose, amitriptyline levels were on average slightly higher for the sustained release product. However, taking all 8 comparisons (in 6 subjects) the mean ratio of 1·09 did not differ significantly from unity ($P \simeq 0{\cdot}3$, d.f. = 7). Table 1 shows that patient VI gave particularly variable ratios, ranging from 0·66 to 1·40; for the other five subjects ratios ranged only from 1·02 to 1·25. The mean of these five values was $1{\cdot}15 \pm 0{\cdot}041$ (s.e.m.), giving $P \simeq 0{\cdot}02$ (2-tail t-test for significance of departure from unity). Amitriptyline levels 12 h after the dose and nortriptyline levels at each time gave mean ratios close to unity and not significantly different from it, whether averaged over all 8 comparisons or over 5 subjects only.

These results suggest that if the absorption of amitriptyline from the sustained release product by these patients was significantly slower than from ordinary tablets, any effect on plasma levels late in the dosage interval was offset by a concomitant reduction in bioavailability. Alternatively, both absorption rate and bioavailability might have been similar for the two formulations.

Single doses of the substained release tablet in healthy subjects have been shown to give very variable rates of absorption of amitriptyline (Burch & Hullin 1981). Some doses were absorbed satisfactorily slowly, some as fast as from ordinary tablets and some at intermediate rates. The average rate was therefore slower, but average bioavailability was also reduced, resulting in equal average drug levels in the plasma 24 h after the dose. The present results for patients in the steady state are thus consistent with those of the single-dose experiments.

Clinical trials (Barton & Snaith 1972; Sedman 1973; Middleton 1976) have shown no significant differences in therapeutic response or side-effects between the sustained release product given once at night and ordinary amitriptyline tablets given three times daily in a total daily dose 50% greater than the sustained release tablets. However, it is not clear what difference in outcome would be expected if groups of patients were treated with the same formulation in doses differing by a factor of 1·5. Nor has the sustained release product been compared clinically with equal doses of ordinary tablets given once at night.

In the present study, Lentizol produced a marginally higher average plasma amitryptyline level 24 h after the dose, but the difference was of doubtful significance. There was no difference in amitriptyline levels at 12 h, nor in nortriptyline at either time. Thus the sustained release product gave no apparent overall advantage over ordinary tablets in maintaining higher plasma drug levels during the latter half of the dosage interval. No pharmacokinetic evidence was obtained that would predict equivalent effects for the sustained release and ordinary tablets of amitriptyline in a dose 50% greater.

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