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Sedative properties of simple analgesics

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1. An attempt has been made to assess under double blind conditions the sedative action of phenacetin, paracetamol, and aspirin by testing their ability to prolong sleep in the face of a rapidly filling bladder.

2. The volume in the bladder on awakening was independent of the rate of urine formation.

3. Although phenacetin prolonged sleep there was no corresponding increase in urine volume on awakening. Apparently phenacetin sensitized the bladder to the distending volume and reduced the rate of urine formation. It was unnecessary to postulate sedative action to explain the results.

4. Paracetamol had no effect on the mean sleep interval or mean urine volume although the drug was not totally inactive since it increased the variance of the results for sleep interval and urine volume.

5. Aspirin prolonged sleep interval, but this effect would be explained if it were an antidiuretic because there was no increase in urine volume on awakening.

6. Apparently no sedative or hypnotic has been shown to increase the urine volume on awakening under similar conditions.

The impression that the simple analgesics have a sedative action is widely held, although we know of only one report (Eade & Lasagna, 1967) in the literature demonstrating this action in man. For the purposes of this paper a sedative is defined as a compound which reduces or delays the response to a non-painful disturbing stimulus.

If healthy subjects drink enough water before going to bed they will be awakened by a full bladder. A drug without antidiuretic action which delays this awakening is a sedative by our definition. A method based on these facts has been used in the past to assess the effectiveness of sleep-inducing drugs (Condouris, Costa & Bonnycastle, 1960; Condouris & Bonnycastle, 1961; Jackson & Gooding, 1964; Isaacs, 1957). The present report is concerned with two separate double-blind trials, the first to test the sedative action of phenacetin, and the second to compare the sedative actions of phenacetin, aspirin, and paracetamol with that of a placebo.

Methods

Ten healthy males, not taking drugs, and between the ages of 25 and 30 years, acted as volunteers. In the first trial a standard water load of 1,100 ml. was given half an hour before they retired, after which most subjects were awakened once only by the stimulus of a full bladder. Before the second trial water loading experiments were conducted to find out how much water was necessary to ensure that each subject was awakened twice during the night.

In this second trial each subject was given a water load of at least twice his bladder capacity so that he should be awakened twice. The water load (between 800 ml. and 2 l.) and tablets were taken together on retiring, immediately after the bladder had been emptied.

The tablets were given in an ordered sequence, neither subjects nor assessor knowing which tablets were active. Subjects received both active tablets and placebo a number of times, each subject acting as his own control. The tablets disintegrated rapidly and were identical in every way except taste. In the first trial 600 mg phenacetin were given, but in the second trial, the dose was adjusted to be as near as possible to 10 mg/kg body weight using whole 300 mg tablets of paracetamol, phenacetin or aspirin.

Subjects recorded the time of taking the tablets and the water load together, the time of being awakened to pass urine and the volume passed. The importance of standardization of routine was stressed (Norris & Nisbet, 1963), particularly with regard to the avoidance of smoking, alcohol, caffeine and exercise. For the second trial each subject drank a water load 2 hr before taking the drug and his stipulated final water load in an attempt to standardize the degree of hydration at the beginning of the experiment. On the following morning subjects recorded their assessment of the time taken to fall asleep and the quality of sleep. The assessment was indicated on a non-graduated 10 cm line, one end representing worst ever, the other best ever, for time to fall asleep and for sleep quality (R. C. B. Aitkin, 1963, personal communication). (Fig. 1.) Results were classified as follows:

1. Sleep interval in hours, being the interval from taking the tablets and final water load to the time of first being awakened to pass urine. Within-subject comparison should show a significant prolongation of this interval by a sedative, provided the stimulus of a full bladder reached threshold within the period of action of the drug.

2. The volume of urine passed when awakened. This enabled the rate of urine formation in response to a standard water load to be calculated, assuming complete

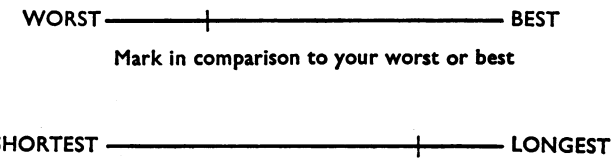

FIG. 1. Lines used for recording quality of sleep and time to fall asleep.

bladder emptying. Any effect of a drug on urine formation could thus be assessed by comparison with a placebo. Increase in urine volume with increased sleep interval was expected.

3. Comparison of the subjective assessment of sleep quality and the time taken to fall asleep were made by measuring the distance of the mark from left hand end of the 10 cm line. The subjective comparisons were analysed by non-parametric methods only.

Analysis of the urine collected at the first awakening in one block of experiments showed traces of the appropriate drug in all subjects except one. Analysis of blood samples from this subject showed the drug to be present in the serum and it is assumed that he is a slow excretor of the drugs concerned.

Results

The effects of the drugs were assessed by sequential testing (Armitage, 1960) and by *t* tests on paired results. Sequential testing would have allowed the experiments to be stopped when a given level of statistical significance had been reached (Figs. 2 and 3) but in fact the full block was completed in the majority of subjects.

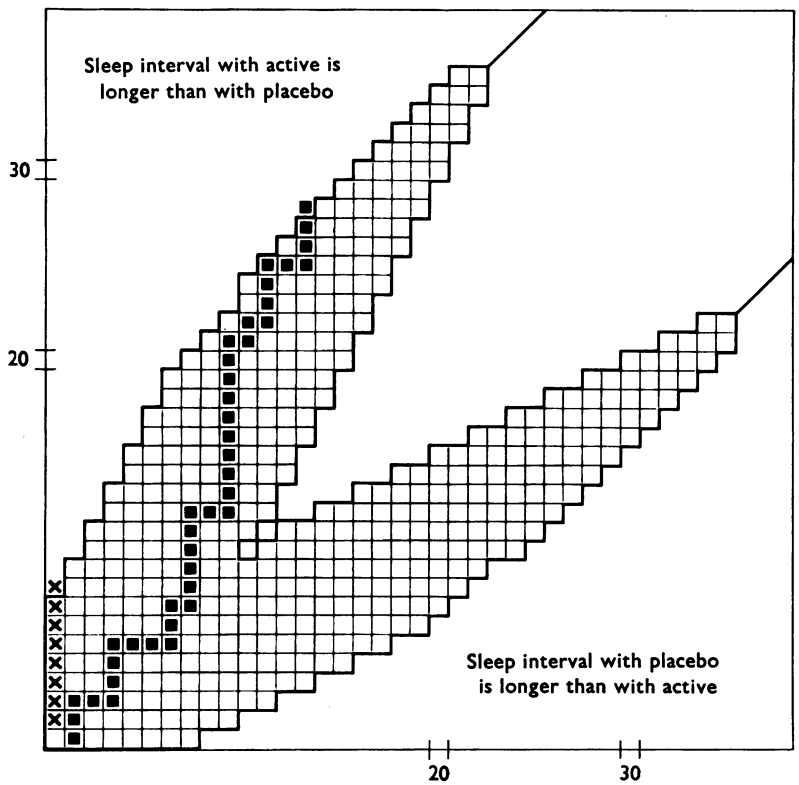

FIG. 2. Sequential analysis of paired results for sleep interval, phenacetin trial 1 (■) and aspirin trial 2 (×). Each dot or cross represents the result of one within-subject paired comparison. When sleep interval was longer after placebo than after phenacetin the next dot was added horizontally; when sleep interval was longer after phenacetin the next dot was added vertically. The series of crosses and dots crosses the upper margin of the leg of the figure indicating that the sleep intervals of sequential pairs of tests with phenacetin and aspirin were longer than with placebo ($P=0{\cdot}05$).

The observed normal distribution of paired differences in sleep interval between active tablets and placebo allowed use of Student's *t* test in evaluating results.

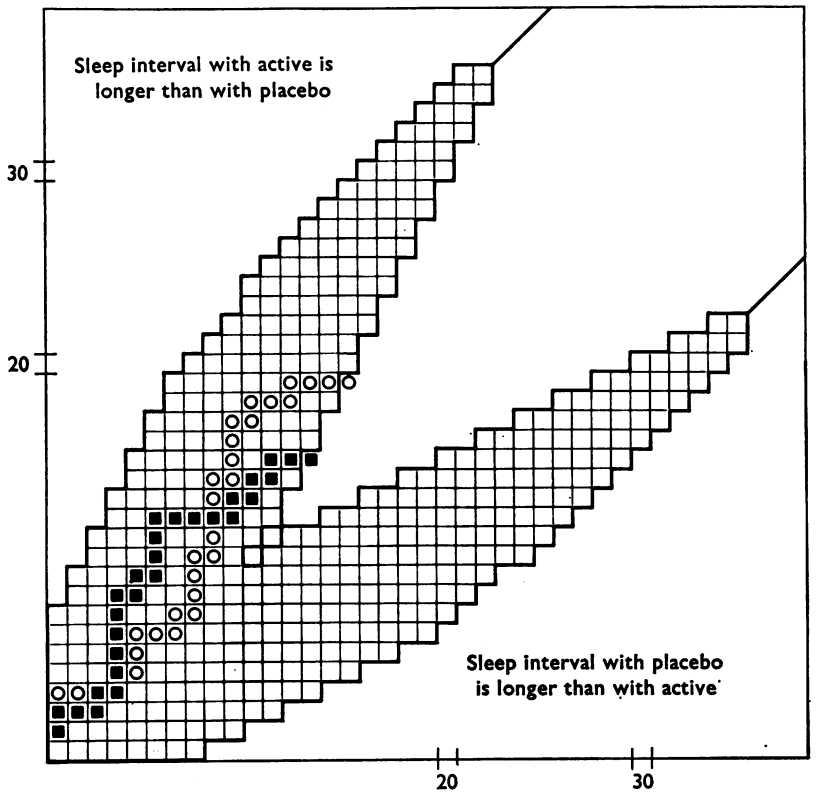

FIG. 3. Sequential analysis of paired results for sleep interval after paracetamol (○) and phenacetin in trial 2 (■). The series of circles and boxes cross the central margin of the two legged figure, consistent with no significant difference in sleep interval between drugs and placebo ($P=0{\cdot}05$).

TABLE 1. *Mean sleep intervals and urine volumes with placebo and active compounds. Statistics based on comparison of sequentially paired results for both trials.*

Number of pairs	Sleep interval			Urine volume		
	Mean	Increase	*P* value	Mean	Increase	*P* value
Placebo	1 hr 23 min			666		
Aspirin		14±5 min	0·02		+9±22 ml.	0·7
n=37	1 hr 37 min			675		
Placebo	1 hr 22 min			657		
Paracetamol		10±6 min	0·1		+26±25 ml.	0·3
n=38	1 hr 32 min			683		
Placebo	2 hr 39 min			638		
Phenacetin 1		30±12 min	0·03		−44±22 ml.	0·05
n=49	3 hr 9 min			594		
Placebo	1 hr 22 min			657		
Phenacetin 2		6±6 min	0·3		+4±22 ml.	0·9
n=38	1 hr 28 min			661		

Phenacetin

Table 1 shows that the mean sleep interval for placebo in the first trial was 2 hr 39 min which was increased by 30 min after 600 mg phenacetin, a result which would be expected by chance only once in thirty repetitions of the trial if phenacetin were inactive. However, the mean urine volume on awakening after phenacetin fell by 44 ml. from 638 ml. with the placebo.

By increasing the waterload in the second trial, the mean sleep interval with placebo was shortened to 1 hr 22 min (Table 1). Sleep intervals in the second trial were all less than 4 hr—that is, within the expected duration of action of the drugs (Brodie & Axelrod, 1949; Goodman & Gilman, 1955). Under these conditions phenacetin changed neither sleep interval nor urine volume (Fig. 3). Either by chance, or because of the actions of phenacetin, there were eight tests out of thirty-eight when the sleep interval was less than 1 hr after phenacetin. This should be compared with seven out of 123 when the drug was either aspirin or paracetamol.

Table 2 shows the variances of sleep times and urine volumes. If the drugs were completely inactive, the variance of the with-drug results would be similar to the variance of the results with placebo. It may be seen that in both trials phenacetin did significantly increase the variance of the sleep times but had no significant action on urine volumes. Thus phenacetin was in some way having an effect on sleep time.

Paracetamol

In contrast to the results with phenacetin, the results with paracetamol (Table 1) lead to clear cut conclusions. The mean sleep interval increased insignificantly by only 10 min S.E. ± 6 min ($P = 0{\cdot}1$) compared with placebo (Fig. 3). The mean volume of urine increased insignificantly by 26 ml. S.E. ± 25 ml. It is quite clear that under our conditions paracetamol had no net influence on sleep interval and urine volume.

TABLE 2. *Variances of sleep intervals and urine volumes for first and second trials.*

Number of pairs	Sleep interval	Variance ratio	*P*	Urine volume	Variance ratio	*P*
Placebo	0·1262			32544		
Aspirin		2·368	<0·01		1·165	>0·05
$n=37$	0·2989			37928		
Placebo	0·1267			35794		
Paracetamol		3·44	<0·01		1·604	>0·05
$n=38$	0·4364			56454		
(Trial 1)						
Placebo	1·156			22782		
Phenacetin		1·730	<0·05		1·171	>0·05
$n=49$	2·001			26685		
(Trial 2)						
Placebo	0·1267			35194		
Phenacetin		2·594	<0·01		1·469	>0·05
$n=38$	0·3287			51686		

Aspirin

It may be seen from Table 1 that the subjects slept 14 min S.E. ±6 min longer after aspirin than after placebo. By sequential testing the sleep interval was also prolonged significantly. However, the urine volume on awakening was neither consistently nor statistically significantly increased.

Subjective comparisons

Subjective assessments of the quality of sleep and the time taken to fall asleep using the line method (R. C. B. Aitkin, personal communication) were analysed sequentially (Armitage, 1960). It can be seen from Fig. 4 that whereas aspirin improved the quality of sleep it did not affect the time taken to fall asleep. Probably subjects were asleep before any drug could be fully effective. However, the quality of sleep was reported as better after aspirin which prolonged sleep interval but not after phenacetin.

When sleep interval and sleep quality were ranked in order there was no correlation except in one subject in the first trial who reported that he often had difficulty in sleeping. All our other subjects habitually slept soundly. This subject did not take part in the second trial which involved aspirin, paracetamol and phenacetin.

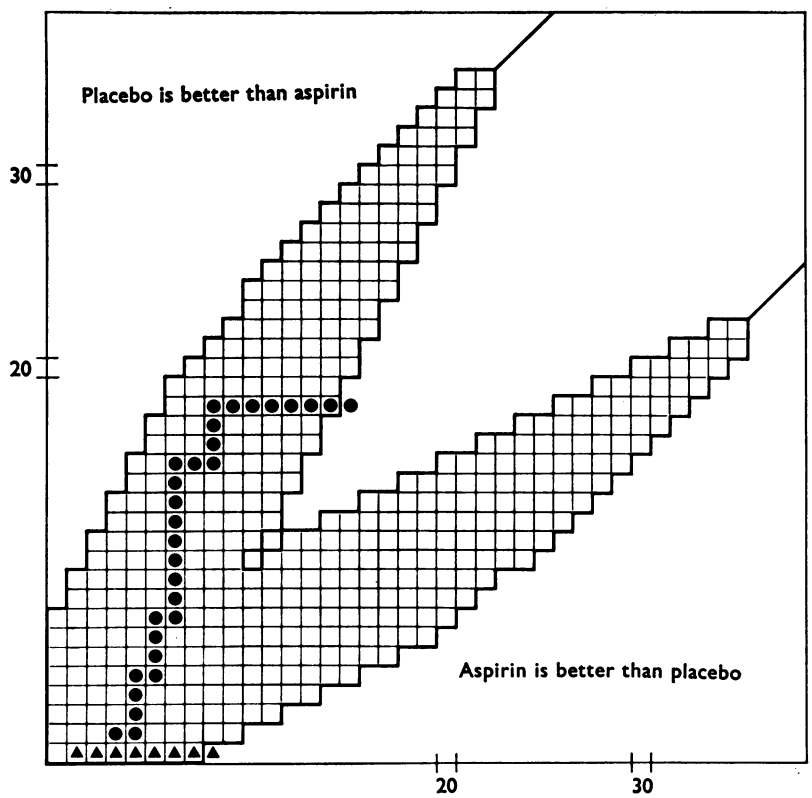

FIG. 4. Sequential analysis of paired results for sleep quality (▲) and time to fall asleep (●) after aspirin. Crosses signifying sleep quality cross the lower margin of the two legged figure, indicating that aspirin significantly improved the sleep quality. Dots signifying time taken to fall asleep cross the central margin showing that there was no difference between placebo and aspirin ($P=0{\cdot}05$).

Discussion

The subjects of the present experiments were colleagues with first-hand experience of the scientific method. We therefore felt confident that they would read the volume in a 1 l. cylinder and record the results. Had we been working with more subjects we should have been content to measure only sleep interval, which was significantly prolonged by both aspirin and phenacetin. Having failed to find in the literature any reference to the proven antidiuretic action of either phenacetin or aspirin we should have come confidently to the conclusion that these compounds were sedatives in that they prolonged sleep in the face of the stimulus of a filling bladder. The results of the measurements of urine volume make this view untenable. Condouris *et al.* (1960) report no significant differences in mean volume between placebo and drugs which prolonged sleep by as much as 1 hr 50 min (Condouris *et al.*, 1960; Condouris & Bonnycastle, 1961); other groups testing hypnotics using a similar stimulus have not reported a significantly larger volume of urine when awakening was delayed (Jackson & Gooding, 1964; Isaacs, 1957).

Phenacetin

At first sight the prolonged sleep interval with phenacetin seemed to be caused by an unexpected antidiuretic effect of the drug. If phenacetin were simply an antidiuretic it would be expected that the subjects would sleep longer but that the volume of urine in the bladder would be the same as it was with placebo. If phenacetin had a sedative action the urine volume on awakening would have been expected to be larger when sleep was prolonged. In fact the volume on wakening was significantly reduced in the first trial.

The assumption here is that the rate of urine accumulation did not influence the volume which awakened the subject. This assumption is justified by the finding that after placebo the mean volume of urine was 638 ml. on awakening after 2 hr

TABLE 3. *Mean sleep intervals and urine volumes after placebo in first and second trials.*

	Mean sleep interval (hr)					Mean urine volume (ml.)		
	First		Second					
Subject	Mean	*n*	Mean	*n*	Difference	First Mean	Second Mean	Difference
S	4·4	4	1·2	4	3·2	625	588	+37
LAN	2·5	6	1·4	5	0·9	585	644	−59
E	2·3	3	1·8	4	0·5	853	892	−39
LAL	2·6	6	1·3	5	1·3	617	610	+7
WE	1·5	5	1·0	5	0·5	405	442	−37
T	3·3	6	1·2	5	2·1	852	841	+11
C	2·2	6	1·8	4	0·4	533	488	+55
WA	2·3	4	1·7	2	0·6	598	670	−72
					$\bar{x}$ 1·2			$\bar{x}$ −12
					S.E. ±0·35			S.E. ±16·3
					t 3·4			*t* 0·74
					$P<0.025$			$P=0.5$

Relation between change of sleep interval and change of urine volume after a placebo in first and second trials:

when x=change in sleep interval (trial 1–trial 2) and y=change in urine volume (trial 1–trial 2)

$y=a+bx$ $b=22·38\pm16·7$ $a=-38·6\pm25$ $t=1·3$

39 min in the first trial, and 657 ml. after 1 hr 22 min in the second trial, the difference in urine volume being statistically insignificant ($P=0{\cdot}5$ by within-subject testing, Table 3), in spite of the difference in the rate of accumulation.

The finding that the subjects in the first trial slept longer after phenacetin, but awakened with a significantly smaller volume of urine, would be consistent with phenacetin being an antidiuretic and at the same time sensitizing the bladder to the volume of urine in it by a facilitating action on some other component linking the bladder to the awakening mechanism. The unravelling of this unexpected complexity was attempted by studying the relationships between urine volume and sleep interval, but without success. There was no overall relationship between change of urine volume and change in sleep interval after phenacetin ; half the subjects showed a negative and half a positive correlation. Possibly the antidiuretic effect of phenacetin is independent of its action as a sedative.

If the local sensitizing action postulated above were operating in the second trial it could explain the failure to demonstrate prolongation of sleep interval by the expected sedative action of phenacetin (Table 1).

Paracetamol

Paracetamol had no net action on sleep interval or urine volume (Table 1). The small standard errors obtained with the thirty-eight pairs of results are grounds for confidence in the method.

Aspirin

Although under our conditions aspirin prolonged sleep interval significantly this could be explained by supposing that it had an antidiuretic action. Increase in urine volume on awakening was insufficient to demonstrate a sedative action (Table 1). With the larger waterload that the subjects received in this second trial, merely increasing the sleep interval by 14 min would be expected to increase urine volume to about $666 \frac{(82+14)}{82} = 780$ ml. In fact the mean volume on awakening was 675 ml. S.E. ± 32 ml.

Experiments have since shown that the rate of urine production under our conditions is constant up to 120 min (M. Jourdan unpublished).

Subjective results

The method for observing subjective effects leaves the subject free to express any shade of opinion rather than having to choose the usual number or phrase to express his feelings (Beecher, 1959). By simple analysis the statistical significance of small differences can be assessed. Using this method of analysis of subjective responses our subjects reported improved quality of sleep with aspirin. It is possible that the absence of any correlation between prolonged sleep interval and improved sleep quality was because we studied a population of normal sleepers.

Others have not found sedation with larger doses of aspirin in subjects who were awake, but suggest that phenacetin acts as a sedative and might improve sleep (Eade & Lasagna, 1967; Wolfe, Hardy & Goodell, 1941). None of our subjects

showed any improvement in sleep quality with phenacetin but in the only subject who had difficulty in sleeping there was a positive correlation between prolongation of sleep with phenacetin and improved sleep quality.

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