THE BLOOD BARBITURATE DURING PROLONGED NARCOSIS.

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G. A. LEVVY in 1940 (*Biochem. J.*, **34**, 73) published from the Department of Pharmacology, University of Edinburgh, a new method for the estimation of barbiturates in blood, claiming that his technique gave results accurate to a 20 per cent. error or less for quantities of 1·0 mgm. or more in 20 c.c. of blood. After studying this method at first hand we have carried out a number of estimations in cases undergoing prolonged narcosis with somnifaine, and studied the blood levels of barbiturates in patients under medication with soluble barbitone and phenobarbitone, a total of 200 estimations having been made.

Using the method for prepared known somnifaine standards we obtained the following figures:

Quantity present.	Estimated quantity.
Nil	*Nil*
0·1	0·12
0·2	0·15

The figures here and throughout this paper represent mgm. per 20 c.c. of blood.

The technique of prolonged narcosis at the Central Hospital involves the administration of a narcotic at four-hourly intervals and either somnifaine, a mixture of allyl-isopropyl and di-ethyl barbituric acids, by intramuscular injection, or a soluble barbitone-phenobarbitone mixture by the mouth, are used. For the purposes of this investigation a very low commencing dose of somnifaine was given as a rule, and each increase in dose was made after it was reasonably certain that a stable blood level had been reached.

The level stabilized for each dose in less than two days unless evidence of toxaemia was present, when the level sometimes continued to rise on a fixed dose for three to eight days, or was still rising when treatment had to be abandoned. Blood for estimation was taken immediately before the 10 a.m. injection, unless the cessation of treatment because of the development of dangerous symptoms indicated a test for some other time. The narcosis was usually pushed until warning signs of possible collapse or impending barbiturate pneumonia appeared.

The first difficulty in the interpretation of results was the general low level of the blood barbiturate, the readings being almost uniformly below 1·0 and more often than not below 0·5. The four-hourly dosage reached when treatment ceased varied from 1·0 c.c. to 3·0 c.c. and averaged 1·75 c.c., that is, 10·5 c.c. in 24 hours. Since this dosage could not have been increased in individual cases without endangering life it is probable that estimations high enough to give a maximum error of 20 per cent. would not often be met, but our results so often gave straight line graphs in uncomplicated cases that we feel they are worthy of record. The graph shows so many nearly straight lines that we consider it evidence both of the reliability of the method, and of the fact that the blood barbiturate level for any particular barbiturate in any individual person is directly proportional to the dose being used, providing that failure to sustain excretion is not producing toxic symptoms.

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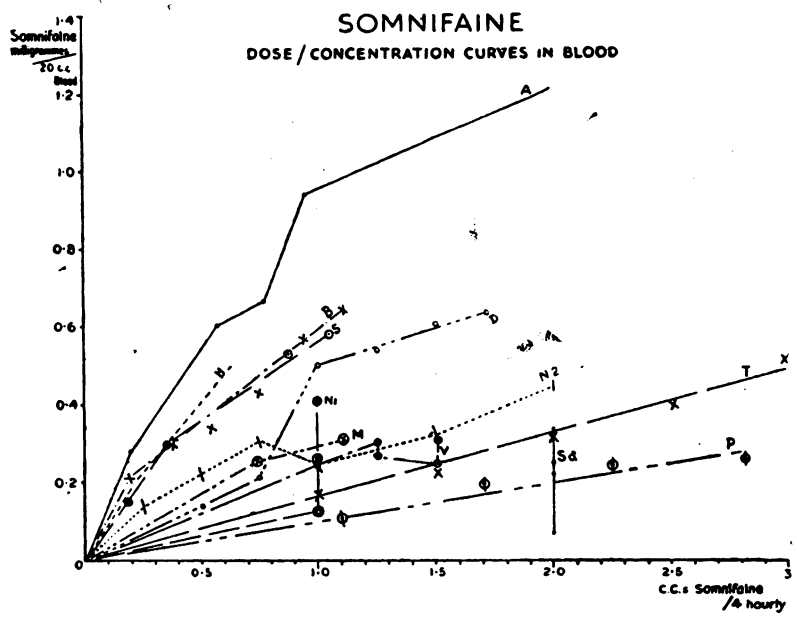

Somnifaine dose per 100 pounds' weight. Capital letters indicate patients' initials. N1 and Sd had a fixed dose, 1·0 c.c. and 2·0 c.c. respectively throughout.

The variation in blood levels was so marked in different patients on the same dose that no standard figures for set circumstances can be given, as the following figures illustrate:

Somnifaine dose four-hourly.	Blood level.	Average.
1·0 c.c. .	From 0·14 to 0·90 .	0·41
1·5 ,, .	,, 0·31 ,, 1·00 .	0·55
2·0 ,, .	,, 0·23 ,, 1·34 .	0·73

Narcosis was smooth with levels from 0·25 to 1·00 and averaging 0·47.

Slight toxicity occurred with levels from 0·16 to 1·00 and averaging 0·41.

Marked toxicity occurred with levels from 0·30 to 1·34 and averaging 0·58.

Our figures suggested that the difference in level between safe and toxic doses varied from 0·00 to 0·40 and averaged only 0·13.

The variability of the toxic level and the small difference between safe and toxic levels mean that one must rely on clinical acumen to direct treatment. In two cases toxic symptoms calling for withdrawal of the drug developed with a blood level lower than one previously found during a smooth narcotic phase and in one of these cases the figures were striking. The patient being comfortable on a dose of 1·0 c.c. four-hourly with a blood level of 0·19 at the first estimation and 0·38 two days later, the dose was raised to 1·5 c.c. four-hourly, and two days later the level was 0·23. Evidence of collapse appeared two days after and the level was found to be 0·16. The large possible error must be remembered, but this particular group of results was so unusual that we incline to the belief that the blood level was actually falling roughly as indicated by the figures.

It is convenient to mention here that the clinical effects of blood levels are not comparable for different barbiturates. A patient was about and active who had been taking 20 gr. of soluble barbitone daily over a long period, and the blood level was 0·44. Following a period without medication a somnifaine narcosis was commenced and the patient became dangerously toxic with a recorded level of 0·31.

The blood somnifaine level cannot be used to forecast the possible duration of smooth narcosis to follow; thus five patients on a dose of 1·0 c.c. four-hourly with blood barbiturate levels of 0·50 or over, average 0·64, continued with narcosis for

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an average of 10·4 days longer, while five patients on the same dose with blood levels of 0·40 or under continued with narcosis for an average of 9·5 more days.

We did not detect any significant changes in the blood barbiturate level during the usual four-hourly interval between doses, an interval previously chosen on clinical experience, but we regard this as a probable illustration of the extent of the experimental error, as the fall following the maximum blood concentration after a dose of barbiturate is probably precipitate at first. There was evidence of a sudden upward swing in blood barbiturate level with the development of severe toxic symptoms, but our estimations under these circumstances were very few. We have noticed distinct falls in blood level after an interval of about ten hours without medication; in one case the level fell from 0·45 to 0·35 in nine hours, to 0·13 two days later and to 0·10 in a further two days. The fall in somnifaine levels appeared rather more rapid than in soluble barbitone levels, a somnifaine reading fell from 0·52 to 0·13 in four days, and a soluble barbitone estimation from 0·44 to 0·19 in the same period. The following table gives results in two other cases:

	1. Somnifaine.	2. Soluble barbitone.
Level when treatment was stopped	0·31	0·30
After 2 days	0·16	—
,, 4 ,,	0·08	0·19
,, 7 ,,	—	0·13
,, 9 ,,	0·03	0·08

The smaller figures are of course greatly suspect. Roughly speaking the blood somnifaine halves itself in one day, is about $\frac{2}{3}$ of its original level in 2 days, and $\frac{1}{4}$ in 4 days; thus averages of four more cases gave—original level, 0·37; after one day, 0·17; after two days, 0·14; and after 4 days, 0·10.

Soluble Barbitone.

A few estimations of the blood barbiturate in patients taking soluble barbitone were made against a soluble barbitone standard, a dose of 20 gr. a day per 100 lb. weight being used. Two patients who had been on this drug for some time gave levels of 0·47 and 0·74. Three others who received the drug for the first time gave the following results:

1st. On the 7th day 0·50 and on the 18th day 0·68, the drug being then withdrawn because of toxic symptoms.

2nd. On the 4th day 0·35, on the 25th day 0·83, on the 33rd day 0·83, and on the 42nd day 1·00, the drug then being stopped for toxic manifestations.

3rd. This patient appeared to strike a clinical equilibrium.

4th day	0·42	mgm. per	20 c.c.
7th ,,	0·72	,,	,,
18th ,,	0·38	,,	,,
25th ,,	0·47	,,	,,
33rd ,,	0·66	,,	,,
54th ,,	0·53	,,	,,

The results are seen to vary from 0·35 to 1·00, the average figure being 0·61.

Phenobarbitone.

A small group of six chronic epileptics on high dosage were investigated, five being men. All had had phenobarbitone for some years, except for an interval on prominal, and all had been back on phenobarbitone for at least six months. Experience with prominal was generally unfortunate, and two men had failed to regain their previous fit control, when returned to phenobarbitone after a deterioration on prominal. It happens that these two gave the lowest figures for blood barbiturate measured against a phenobarbitone standard. No correlation of blood level with weight, age, blood pressure, pulse pressure, diastolic or systolic pressures, sedimentation rate or blood urea could be found.

Case 1.—On six grains of phenobarbitone daily for three years; previously on four grains or seven grains of prominal. Fit incidence three per month on all doses, but patient most comfortable on present dose. Blood barbiturate level 0·43.

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CASE 2.—On six grains daily for two years; previously on four grains or six grains of prominal. Fits rare and least on present dose. Level 0·36.

CASE 3.—On six grains daily for three years; previously dose had varied from four to nine grains. Fit incidence four per month on all doses, but feels best on present dose. Fits were very numerous over a period on nine grains of prominal daily. Level 0·26, repeated with the same result.

CASE 4.—On six grains daily for one year and had had three fits during that period; previously on four grains daily and then having about five fits a month. Level 0·15.

CASE 5.—On four grains a day was having two fits a month, but fits became very frequent on prominal six grains a day. During the next four years the original control was never regained, and fits have averaged over three a month, and the dose has been six grains of phenobarbitone daily for some time. Level 0·07. The dose was increased to nine grains a day for a period and the level rose to 0·15.

CASE 6.—Fits were rare on six grains of phenobarbitone daily. A change to nine grains of prominal had to be stopped after one month because of the great increase in fits, and thereafter six grains of phenobarbitone rising to nine grains daily failed to obtain the original control. Results at weekly intervals were: 0·06, 0·11, 0·13, 0·06, and 0·08. Repeated a year later the level was 0·20.

The features of this series are the individual variation and the smallness of the blood level in certain cases.

SUMMARY.

A new method for the determination of barbiturate in blood has been tried with a view to estimating its clinical use in prolonged narcosis and other barbiturate treatments.

Owing to wide individual variations in tolerance and rates of destruction or excretion, the estimation is of little use in clinical practice, and information obtained for medico-legal purposes would have to be interpreted very widely.

The blood levels for different barbiturates are not comparable.

The blood level for a particular drug in the same individual is directly proportionate to the dose unless the excretory mechanisms are being overwhelmed, when toxic symptoms are accompanied by a sharp rise.

Our thanks are due to Dr. G. A. Levvy for his instructions concerning the method of estimation, and to Messrs. Roche Products Ltd. for supplies of barbituric acids for making somnifaine standard solutions.

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