Psychopharmacologia (Berl.) 9, 73—77 (1966)

The Hypnotic and Sedative Effects of *3-Methyl-3,4-Dihydroxy-4-Phenyl-Butin-1, a Two Phase Investigation Employing Double Blind Techniques and Sequential Analysis

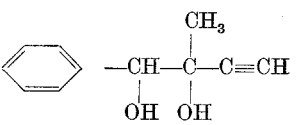
S. G. Flavell Matts

Royal Hospital, Wolverhampton

Received July 7, 1965

It is important to investigate clinically any promising new sedative or hypnotic drug because tolerance and effectiveness of existing sedatives are so variable from patient to patient. Although barbiturates are the most widely used and often the most effective group of agents in this field, they have a number of serious disadvantages including drug rashes, variability of effect from patient to patient, marked "hangover" effects and production of mental confusion in the elderly patient. In view of this the door is always open for improved and safer hypnotic preparations.

3-methyl-3,4-dihydroxy-4-phenyl-butin-1 (3 M.D.P.B.) is a hypnotic and sedative preparation that has been developed, tested and clinically used widely in Germany. It has been extensively examined pharmacologically and shown to combine sedative and hypnotic effects with a low toxicity and freedom from teratogenic effects; in addition chronic toxicity tests in animals showed no adverse effects (Kuhn and Wick, 1963; Wurmbach, 1963). Chemically it is crystalline, optically inactive, practically odourless and soluble in water 7—8%. Molecular weight is 176. It is not related chemically to barbiturates though it is related to methylpentynol.



3-methyl-3, 4-dihydroxy-4-phenyl-butin-1.

Clinically, studies of 3 M.D.P.B. have revealed that a dose of 750 mgm can be effective as a hypnotic and 250 mgm as a day time sedative (Broglie, 1963; Messerich, 1963; Schanz, 1963; Gietz, 1963) and

* 3-Methyl-3,4-dihydroxy-4-phenyl-butin-1 = Centalun® (C. H. Boehringer Sohn, Ingelheim am Rhein).

therefore these were the doses chosen for this trial. As one normally uses drugs of this type both as a sleeping preparation at night and also often as a day time sedative in tension anxiety states, it was felt that both these aspects should be explored.

Phase I

In this phase 3 M.D.P.B. was compared with a placebo in identical tablet form. The trial was carried out using a double blind technique as this has been found to overcome many objections and errors that arise in clinical trials and which may invalidate the results (MATTS, 1960). The results were analysed statistically by the well known technique of sequential analysis which has the advantages of making the results available quickly, and of shortening the trial by economy of patients required. Techniques of sequential analysis are described fully in other earlier papers (SNELL and ARMITAGE, 1957; WATKINSON, 1958; MATTS, 1960). The exact design used in this trial was the same as that previously used in other trials (MATTS, 1960; MATTS et al., 1965).

Method. The patients were all general medical patients suffering with a multitude of non-painful medical conditions; those with pain were excluded as this would introduce an unpredictable variable into the analysis. They were allocated by a predetermined random numbers system to either 3 M.D.P.B. or a placebo made up in identical tablet

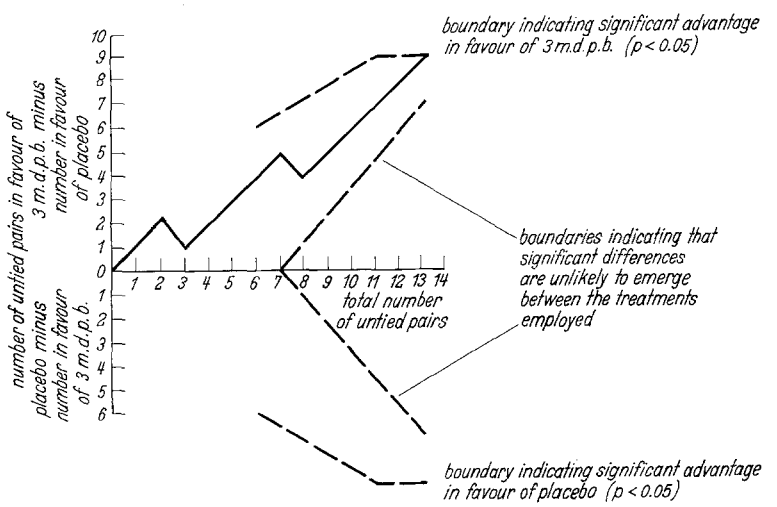


Fig. 1. Sequential analysis chart comparing hypnotic action of 3 M.D.P.B. with that of placebo. Outcome of treatment in untied pairs start at point 0. (—) For each untied pair favouring 3 M.D.P.B. the line is drawn diagonally upwards towards the upper limit of the chart, and for each untied pair favouring placebo diagonally downwards towards the lower limit of the chart. As soon as the control line (———) intersects one of the marked boundaries (— — —) the conclusion marked on the chart for that boundary is proven within the limits of statistical accuracy for this method ($P < 0.05$)

form. The dosage was three tablets, each one either containing 250 mgm of 3 M.D.P.B. or a placebo of equivalent taste.

The patients were treated for 10 consecutive nights to get an overall picture of the effect of treatment. Evaluation was made each morning of the patients and they were classified into either "slept well" or "slept badly"; this being based on the observations of the night nursing staff and the medical staff. The number of good nights were counted up and a score made out of 10 for each patient. Side effects were noted and recorded. The patients were then paired according to the predetermined pairing system and the results plotted on the sequential graph (Fig. 1).

Results. The sequential analysis allowed the trial to be stopped at 26 patients at which point the boundary indicating a significant advantage to 3 M.D.P.B. was reached. No side effects occurred in this series of patients.

This shows conclusively that 3 M.D.P.B. in a dosage of 750 mgm possesses hypnotic properties.

Phase II

In this investigation the sedative effects of 3 M.D.P.B. were evaluated by comparing it with a well tried day time sedative, Phenobarbitone.

Method. The patients were all outpatients suffering with recognisable tension anxiety states of the type known to benefit from sedatives. They were allocated in a randomised order to either tablets of 3 M.D.P.B.

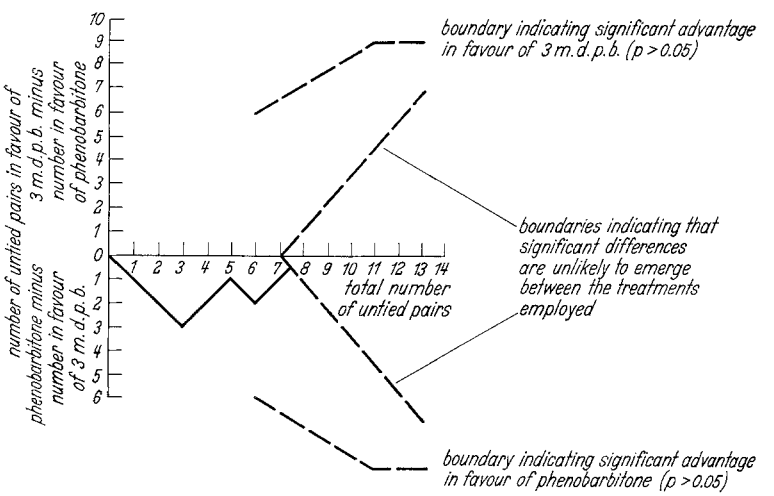


Fig. 2. Sequential analysis chart comparing sedative action of 3 M.D.P.B. with that of phenobarbitone. Outcome of treatments in untied pairs start at point 0 (—). For each untied pair favouring 3 M.D.P.B. the line is drawn diagonally upwards towards the upper limit of the chart, and for each untied pair favouring phenobarbitone, diagonally downwards towards the lower limit of the chart. As soon as the control line (———) intersects one of the marked boundaries (———) the conclusion marked on the chart for that boundary is proven within the limits of statistical accuracy for this method ($P < 0.05$)

250 mgm, or phenobarbitone 30 mgm. These doses being chosen as they have been used for some time and are generally felt to be clinically effective. The tablets were given three times daily (a daily dose of either 750 mgm 3 M.D.P.B. or 90 mgm phenobarbitone) for a total continuous period of three weeks.

The patients were examined and assessed at the beginning and end of the trial and were classified at the end of the trial as either better, same or worse from the point of view of their tension anxiety state. The results were then compared by the predetermined randomised pairing code and were plotted onto the sequential analysis graph (Fig. 2) using the same methodology as described in Phase I. In each group one patient developed a slight drug rash but this did not necessitate stopping therapy.

Results. It can be seen from the Fig. 2 that no significant advantage emerged to either 3 M.D.P.B. or phenobarbitone in this trial, and this result was obtained after 16 patients had been included in the trial. Side effects in these patients were scanty and only consisted of slight drug rashes, one patient in each group being affected.

Discussion and Conclusions

Phase I. In the dosage of 750 mgm nightly 3 M.D.P.B. has been shown to be more effective in inducing sleep that a placebo. The results are statistically significant ($P > 0.05$). Side effects were not encountered during treatment in a small but carefully studied group of 26 patients.

Phase II. No advantage to 3 M.D.P.B. was shown when it was compared with phenobarbitone in tension anxiety states. An equal number of side effects occurred in each group.

When carrying out trials of new sedative and hypnotic drugs the most important questions to answer are the effectiveness of the preparation, the immediate side effects and the long term results of using the drug. The first two questions are answered in the phase conclusions above and the third can only be answered by a large series of patients examined over a period of time in great detail, as described recently (Matts et al., 1963).

3 M.D.P.B. appears to have a place in drug therapy as a night time hypnotic without the disadvantages on the elderly of the barbiturates. Further study would determine its exact place in therapeutics in comparison with other hypnotics.

Zusammenfassung

Mittels modifizierter Sequenzanalyse wurde 3-Methyl-3,4-hydroxy-3-phenyl-butin-1 hinsichtlich seines hypnotischen Effektes in einer Dosierung von 750 mg doppelblind vergleichend gegen Placebo untersucht.

Die hypnotische Wirkung von 3-Methyl-3,4-dihydroxy-3-phenyl-butin-1 ist der Wirkung des Falsumpräparates statistisch signifikant überlegen.

Im gleichen Sinne wurde 3-Methyl-3,4-dihydroxy-3-phenyl-butin-1 hinsichtlich seines sedativen Effektes in einer Dosierung von dreimal täglich 250 mg doppelblind vergleichend gegen 3 · 30 mg Phenobarbital untersucht. Bezüglich der sedativen Wirkung der verglichenen Substanzen läßt sich mit der angewandten Methode kein statistisch signifikanter Unterschied erkennen.

Die Ergebnisse werden kurz diskutiert.

References

Broglie, M.: A new barbiturate-free hypnotic which can be repeated. Med. Klin. **58**, 841—842 (1958).

Gietz, E.: Sedative therapy and the treatment of Insomnia. Ärztl. Praxis **15**, 1338—1341 (1963).

Kuhn, F. J., and H. Wick: Pharmacological properties of 3 M.D.P.B. Arzneimittel-Forsch. **13**, 728—734 (1963).

Matts, S. G. F.: Local treatment of Ulcerative colitis with prednisolone-21-Phosphate-Enemata. Lancet **1960 I**, 517—519.

— C. H. J. Swan, and J. Kellehher: Double-blind trial of bismuth aluminate and magnesium trisilicate in peptic ulceration with simultaneous gastric analysis. Brit. med. J. **1965 I**, 753—756.

—, and B. A. Wharton: An assessment of the value of trichlorethyl phosphate in night-sedation. Brit. J. clin. Pract. **17**, 511—513 (1963).

Messerich, J.: Our experiences with the sedative and hypnotic drug Centalun in patients with cardiovascular disease. Ther. d. Gegenw. **102**, 579—580 (1963).

Schanz, G.: The use of the hypnotic and sedative drug Centalun; therapeutic results from the gynaecological clinic. Med. Mschr. **17**, 309—310 (1963).

Snell, E. S., and P. Armitage: Clinical comparison of diamorphine and pholcodine as cough suppressants by a new method of sequential analysis. Lancet **1957 I**, 860—862.

Watkinson, G.: Treatment of ulcerative colitis with topical hydrocortisone sodium, a controlled trial employing restricted sequential analysis. Brit. med. J. **1958 II**, 1077—1082.

Wurmbach, H.: Investigations into the action of 3 M.D.P.B. (Substance Kö 339) on chicken embryos. Ärztl. Forsch. **17**, 383—391 (1963).

S. G. Flavell Matts, M.B., M.R.C.P.E., M.R.C.S.
The Royal Marsden Hospital
London, S.W. 3 (Great Britain)